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CROSSED ATROPHY OF THE CEREBELLUM

PATHOLOGIC STUDY OF A CASE

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CHICAGO

As definite, independent morbid entities, atrophies of the cerebellum are probably more common than inflammations, degenerations or tumors of this organ. Like tumors, cerebellar atrophies may be circumscribed, and like inflammatory or degenerative conditions they may be concomitant manifestations of atrophies elsewhere in the central nervous system. The best known and fairly well studied form of cerebellar atrophy has been described as tardy or late atrophy, predominantly of the cerebellar cortex (Marie, Foix and Alajouanine [1]). It is also known as sclerotic atrophy of the cerebellum, as lamellar and primary parenchymatous cerebellar atrophy and by other names.[2] Atrophies of the cerebellum that are associated with atrophies elsewhere in the central nervous system are represented by a number of pathologic entities of which the best known are crossed, olivopontocerebellar and olivorubrocerebellar. However, they cannot be differentiated clinically, though pathologically they are fundamentally alike, differing from one another only in the extensity and localization of the lesions. In the present case, for instance, the histologic changes in the cerebellum much resembled those seen in the sclerotic atrophy of this organ but were associated with changes in the contralateral cerebral hemisphere.

REPORT OF CASE

History.—A Negress, aged 28, was admitted to a medical ward of the Cook County Hospital on April 22, 1933, because of cough, precordial pain and a "sore throat." One month previously, the patient had been in the hospital for

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1. Marie, P.; Foix, C., and Alajouanine, T.: De l'atrophie cérébelleuse tardive à prédominance corticale (atrophie parenchymateuse primitive des lamelles du cervelet; atrophie paléocérébelleuse primitive), Rev. neurol. **38**:849 and 1082, 1922.

2. Hassin, G. B.: Sclerotic Atrophy of the Cerebellum: Report of Two Cases, Arch. Neurol. & Psychiat. **31**:1205 (June) 1934.

polyarticular arthritis, fibroid tumor of the uterus and a syphilitic cardiac disease. Examination revealed a temperature of 102 F., a pulse rate of 148 and a respiratory rate of 48. The blood pressure was 166 systolic and 52 diastolic. The pupils were large and reacted sluggishly to light and in accommodation. The face was "turned" stiffly to the left, and the musculature of the neck was tender. The right upper extremity was paralyzed; it exhibited a paralytic deformity, a coarse

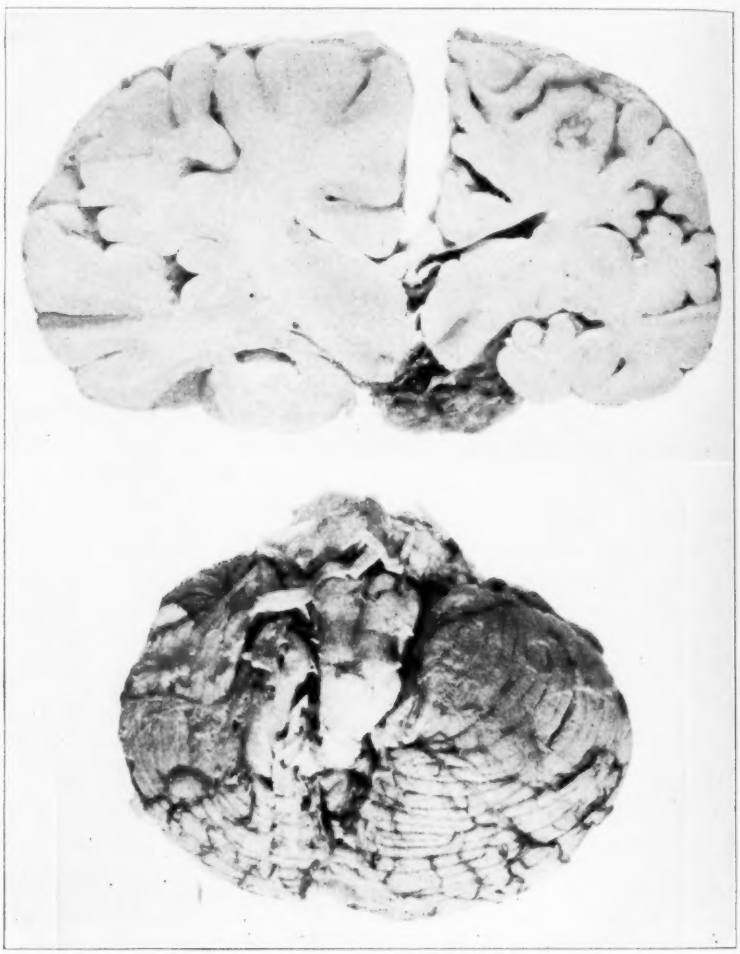

Fig. 1.—The left hemisphere (in the upper picture) is smaller than the right. The left subcortical structures, including the basal ganglia, are also reduced in size. The lower photograph shows the opposite cerebellar hemisphere atrophied.

tremor and diminished muscle tone; the thumb was flexed and opposed to the little finger, and the wrist was swollen. The tendon reflexes were present, without pathologic signs on either side.

The lungs revealed "harsh" râles; the heart was enlarged and exhibited a systolic thrill over the whole precordium, associated with a soft systolic apical murmur. Because of the patient's serious cardiac and pulmonic condition, which

within two days caused death from septic bronchopneumonia (type III), a thorough neurologic examination was evidently out of the question.

Necropsy was performed by Dr. Richard Jaffé.

Gross Observations at Necropsy.—Examination showed: deformity of the mitral and aortic valves with recent verrucous eruptions; hypertrophy and dilatation of the left ventricle of the heart; interstitial myocardial fibrosis with single Aschoff bodies; compression atelectasis of the lower pulmonary lobe; acute septic

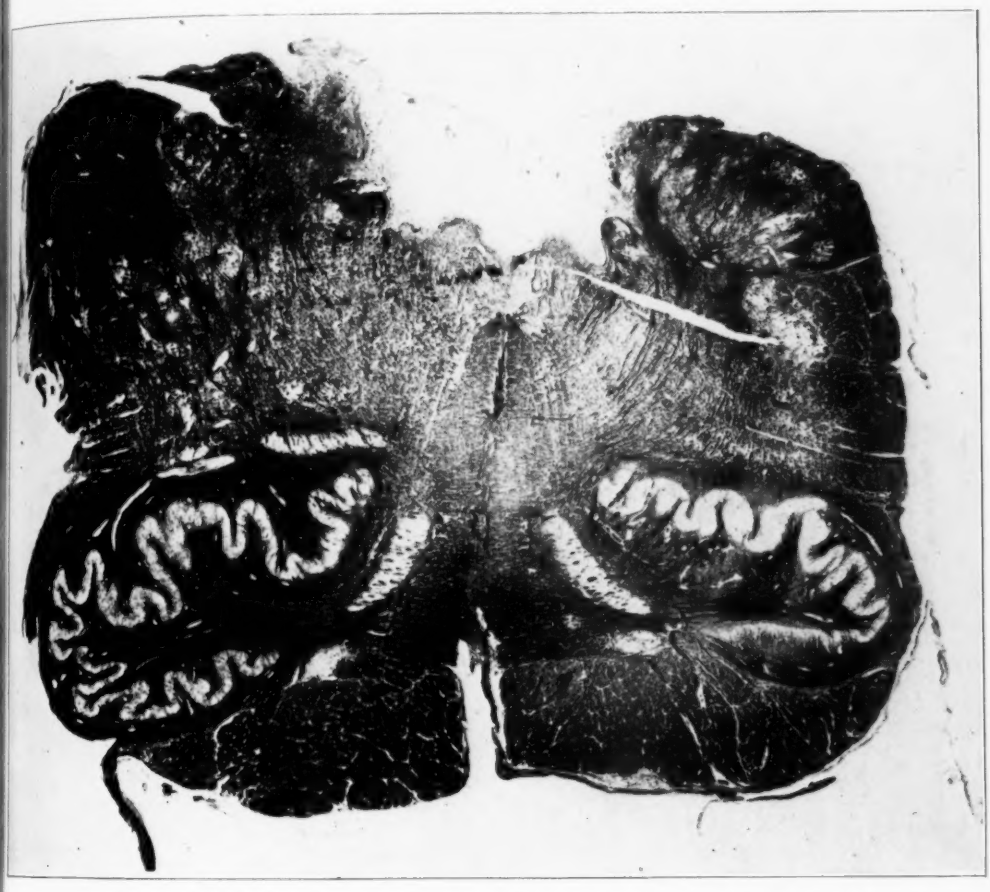

Fig. 2.—Section showing atrophy of the right half of the medulla, including the olives. (Weigert-Pal's stain.)

tumor of the spleen; parenchymatous degeneration of the myocardium; atrophy of the right upper extremity, with palmar flexion of the hand and "ulnar deviation of the fingers;" deformity of the right thumb at the metacarpophalangeal joint, and atrophy of the left cerebral hemisphere.

The brain weighed 910 Gm. The left hemisphere (fig. 1) was smaller than the right; its cortex measured 1.5 mm., and that of the right hemisphere, 2 mm.; the gyri were narrowed; the sulci were deep and bridged by a thickened arachnoid;

the occipital and frontal lobes were especially involved. Atrophy was present also in the ipsilateral basal ganglia, nucleus ruber and pons, especially in its left half, and in the medulla (fig. 2). The left lentiform nucleus, for instance, measured 22 by 9 mm.; the right, 26 by 11 mm. No measurements have been recorded of the occipital lobes, but, as figure 3 shows, the gyri of the left lobe (lower picture) were considerably smaller than those of the right (upper picture). The frontal lobe, however, was equally atrophied on both sides.

The cerebellum (fig. 1) exhibited atrophy of the right hemisphere. It measured 14 by 6.5 by 5 cm., in contrast to the left hemisphere, which measured 19 by 7.5 by 7 cm. Even macroscopically it was possible to discern that the laminae of the right cerebellar hemisphere were narrower, especially those of the digastric, gracile and quadrilateral lobules, while the lamellae of the semilunar lobules appeared to be of normal volume.

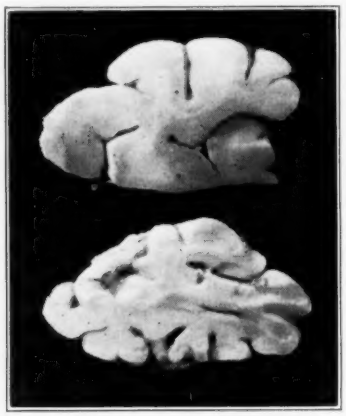

Fig. 3.—The upper section is from the normal structure; the lower section is from the atrophied occipital lobe.

Microscopic Observations at Necropsy.—In sections fixed in pyroxylin and stained by the method of Weigert and Pal, some lamellae of the atrophied cerebellar lobe appeared either unstained or poorly stained. Some, including the Purkinje cells and their processes, were stained normally (fig. 4). In sections stained with toluidine blue or by similar methods, the architecture of the cerebellum exhibited considerable changes. Thus, in some leaflets the Purkinje cells and the ganglion cells of the molecular and granular layers were missing (fig. 5). The only cell bodies present were the glia cells of the Bergmann layer, which are normally situated between the molecular and the granular layer. In figure 5 this layer is represented by archlike bands (B B B) in the left half of the picture. In the right normal half it shows the intensely stained Purkinje cells, which are partly covered by the dense granular layer. Mossy and climbing fibers were either absent or scarce and replaced by bands of glia fibers. The latter followed the distribution and course of the destroyed nerve fibers (fig. 6), which they replaced (at *M*). A similar transformation of degenerated nerve fibers into glial tissue was present in the white substance of the atrophied lamellae. With the molecular and other

layers of the cerebellum they were transformed into a glia tissue scar with the preservation of the general outline and form of the destroyed parts—isomorphous gliosis.

Practically similar, but much milder, changes were present in the lamellae that were only partly destroyed. In such lamellae the Purkinje cells were present but were scarce, and some were reduced in size, and appeared shrunken, fragmented and homogeneous. The nuclei of the majority of the ganglion cells were poor in chromatin, of which only few darkly stained granules were in evidence (hyperchromatosis). In brief, chromatolysis and sclerosis of the cells were the

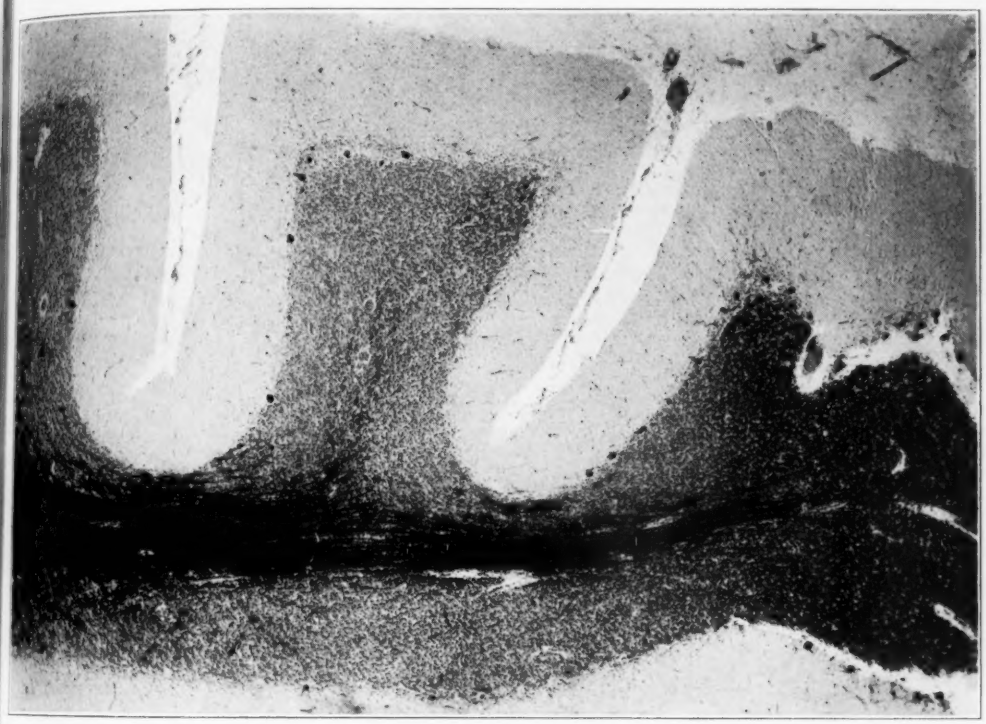

Fig. 4.—The two left atrophied lamellae are poor in nerve fibers, granular and Purkinje cells. The leaflet to the right is normal. (Weigert-Pal's stain.)

outstanding cellular changes in the lamellae that were only partly affected. The nerve fibers—mossy and climbing—were more numerous and were also well seen in sections (especially frozen) stained by modifications of the method of Weigert and Pal.

Equally noteworthy were the changes in the lamellae that under low magnification appeared normal. Under higher magnification, the molecular and granular layers of such lamellae revealed numerous cytoplasmic astrocytes, some of which were large and possessed vacuolated cytoplasm. Their large and granular processes were intermingled with tumefied prolongations of the Purkinje and stellate cells, the Golgi cells of type II of the granular layer and its mossy nerve fibers.

The white substance of such partly affected leaflets appeared normal in sections stained by the method of Weigert and Pal or of Bielschowsky (figs. 4 and 6), but it contained numerous astrocytes and blood vessels, the walls of which often showed proliferated adventitial cells filled with pigment granules. Under higher magnification, the changes in the white substance differed little from those of the molecular layers; that is, it exhibited numerous cytoplasmic glia cells which were present in every leaflet studied. They were present also to some extent in the vermis, where they were very mild. The right nucleus dentatus, which, as noted, was macroscopically smaller than the left, showed no particular microscopic changes. Some of its ganglion cells, including their processes, were tume-

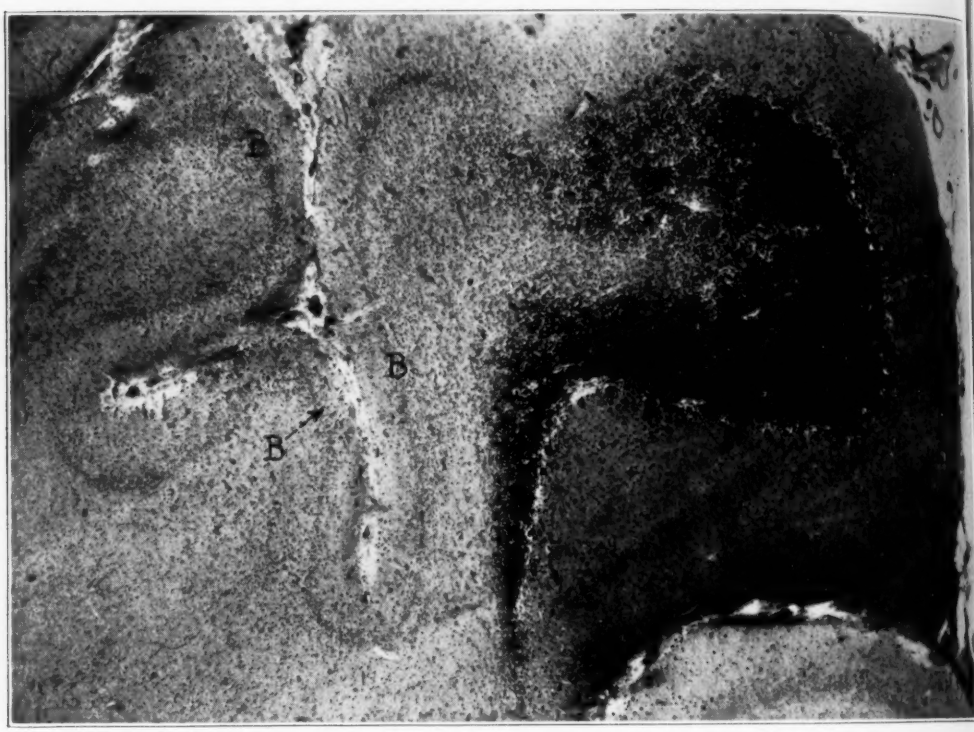

Fig. 5.—The darkly stained leaflet to the right is normal; the two to the left are atrophied. The archlike bands are Bergmann's (B B B) glia cells. Other explanations are made in the text. (Toluidine blue stain.)

fied, but the hilus and the adjacent white substance were markedly vacuolated and rich in astrocytes and amyloid bodies. In general, the changes were like those of the apparently healthy leaflets already described. The same may be said of the white substance of the cerebellum and of the pons, especially in its right half, and the corpora quadrigemina, where, in addition, vascular proliferation was in evidence, but without infiltrative or other inflammatory phenomena. In the red nucleus, optic thalamus and corpus striatum only occasional cell changes were present, but they were very mild, mainly in the form of cellular tumefaction without signs of satellitosis, neuronophagia or reactive glial proliferation, which

were so marked in the cerebellum and pons. Equally mild were the changes in the brachia, olivary bodies and medulla oblongata, regardless of the fact that they were reduced in size.

Changes in the Cerebrum: As stated, the left cerebral hemisphere was atrophied throughout, while in the right hemisphere only the frontal lobe exhibited marked atrophy. The foregoing parts revealed definite changes under the micro-

Fig. 6.—*M* indicates a molecular layer represented by isomorphous gliosis; below is the granular layer bordering on the darkly stained white substance of the cerebellum. (Bielschowsky stain.)

scope. The ganglion cells usually appeared vacuolated and shrunken, sometimes homogeneous and in a state of chromatolysis; the nuclei were poor in chromatin, of which in many cases only a few intensely stained granules were left. Few ganglion cells were normal, and phenomena of satellitosis and neuronophagia were not unusual. In the much atrophied occipital lobe and the motor center for the right arm (fig. 7) the changes were more intense. The cortical

layers exhibited a scarcity of ganglion cells, among which the cells of Betz were absent. Some areas (*A A*) were entirely devoid of cell elements (avascular areas), while the molecular layer was in some places considerably depressed (*P*). Many ganglion cells were pale and entirely devoid of chromophil substance; their nuclei were in a state of karyolysis, and some ganglion cells (in the motor area) were dislocated. In addition, astrocytes were much in evidence, especially in the deeper layers, and blood vessels, some newly formed, were not uncommon. It is noteworthy that similar but milder cortical changes could be demonstrated in the opposite hemisphere, the parietal and occipital lobes, for instance.

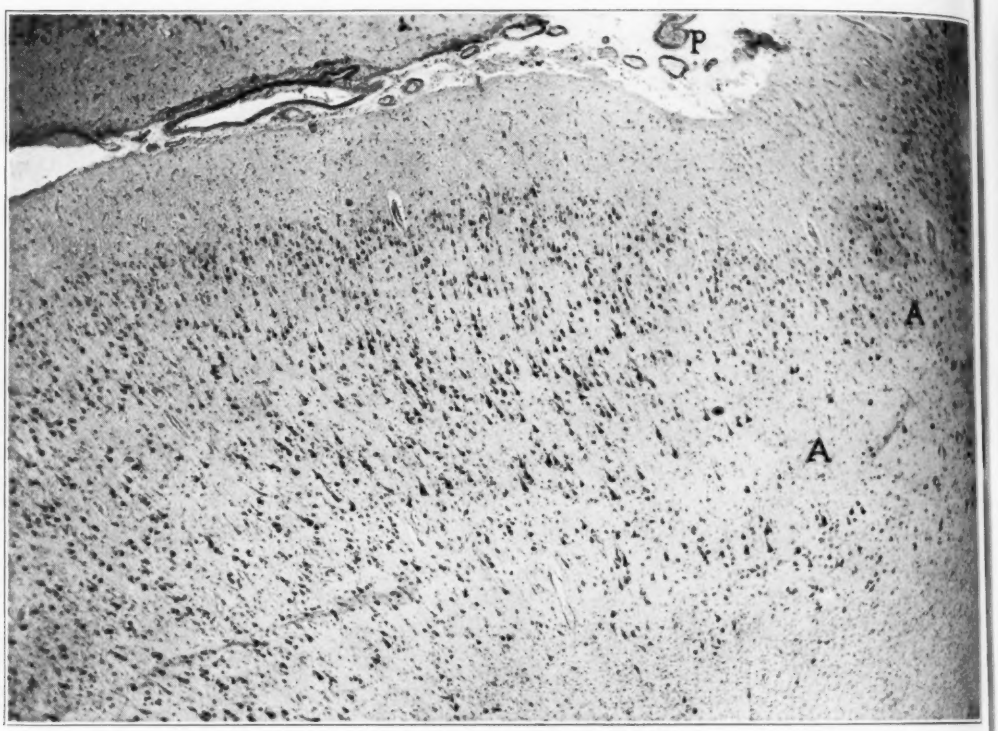

Fig. 7.—Section from the left precentral area of the right arm. The molecular layer is depressed at *P;* the ganglion cells are less dense than normally, and in the third and partly in the second layer avascular areas (*A A*) are present. (Toluidin blue stain.)

Changes in the Pia-Arachnoid: Around the cerebellum, the pia-arachnoid was generally normal, but over the cortex, especially that of the atrophied hemisphere, it was hyperplastic. The subarachnoid space was patent and much dilated over the atrophied areas and resembled the condition seen in external hydrocephalus. In some places it contained numerous cell bodies, fibroblasts mixed with histiocytes, many mesothelial cells and a few lymphocytes.

Summary of the Microscopic Changes.—The changes described can be summed up as sclerotic atrophy of some lamellae of the right cere-

bellar hemisphere, mild degenerative nerve and cell changes in the remaining parts of the cerebellum, manifestations of scattered nerve degeneration in the pons, especially its right half, advanced cellular changes in the left occipital, motor and frontal areas and a practically normal condition of medulla, nucleus dentatus, nucleus ruber and superior cerebellar peduncles.

COMMENT

The histologic changes were especially advanced in the cerebellum, where they resembled those described in late atrophy of the cerebellar cortex (sclerotic atrophy of the cerebellum). Crossed atrophy differs from the latter in the presence of additional, diffuse changes not only in the cerebellum but through the larger portion of the brain. In many areas the parenchymatous changes were manifest in the form of an increased number of astrocytes, which were scattered singly or in groups among the nerve fibers and in the gray substance. As they were especially numerous in the atrophied cerebral cortex, pons and cerebellum, it would be proper to assume that the degenerative phenomena extended mainly along the corticopontile and pontocerebellar pathways. That is to say, the pathologic process evidently originated in the cerebral hemisphere and affected some parts of the contralateral cerebellar hemisphere secondarily. In favor of such an assumption is the fact that while cerebral atrophy is known to cause a contralateral cerebellar atrophy, the reverse is not the fact. For instance, von Monakow [3] observed atrophy of the cerebellar hemispheres in new-born dogs and cats after ablation of the contralateral cerebral hemisphere. The galvanometric experiments of Leon Meyers [4] on animals also demonstrated the contralateral preponderance of the cerebral over the cerebellar hemisphere, which is also proved by many clinical facts. In patients with sclerosis or with absence of the cerebellum, contralateral cerebral lesions are not observed, as is illustrated by the case of a patient of Strong,[5] a child aged 3 years and 4 months. This patient showed almost complete absence of the left cerebellar hemisphere, including the left dentate nucleus, but no apparent asymmetry of the contralateral frontal lobe was present. Neither does every cerebral lesion, however extensive or old, cause cerebellar atrophy. Only when the cerebral lesion occurs in a very young person may atrophy of the cerebellum be expected. Such lesions may be cysts, old inflam-

3. von Monakow, C.: Experimentelle und pathologisch-anatomische Untersuchungen über die Haubenregion, den Sehhügel und die Regio subthalamica, Arch. f. Psychiat. **27**:1, 1885.

4. Meyers, I. L.: Galvanometric Studies of the Cerebellar Function, J. A. M. A. **65**:1348 (Oct. 16) 1915.

5. Strong, O. S.: Preliminary Report upon a Case of Unilateral Atrophy of the Cerebellum, J. Comp. Neurol. **11**:60, 1901.

mations or porencephalic defects. They do not endanger life, which may continue for many years in spite of severe involvement of both the cerebrum and the cerebellum. In some cases the condition lasted thirty-six years (case of Lhermitte and Klarfeld [6]) or even fifty years (cases of Cornélius [7] and Reitsema [8]). Lhermitte and Klarfeld's case was one in which encephalitis had been present since the patient was 3 years of age, while in the cases of Cornélius, Reitsema and Grilis [9] the affected part of the hemisphere of the brain was transformed into a cyst filled with fluid. In other instances the cerebral changes were only microscopic (case of Major [10]) and the cause was looked for in vascular disturbances (Cramer,[11] Kotschetkowa,[12] Mott and Tredgold [13]), while Claude and Loyez [14] even spoke of the possibility of the atrophy being functional, owing to the lack of motor stimuli from the Betz cells to the cerebellum because of cortical cerebral lesions. I could not determine the nature of the cerebral lesion in my case, in which a vast atrophy of the brain was present with definite microscopic changes in the cortical ganglion cells. The changes were not syphilitic; they were not due to other chronic inflammatory or vascular causes, nor was the atrophy of the type seen in amyotrophic lateral sclerosis, in which only the motor ganglion cells are involved. The cell changes were diffuse and much more extensive; they were unquestionably due to some degenerative process, which manifested itself clinically as paralysis and deformity of the right upper extremity. Whether the tremor and hypotonia, which may be of cerebellar origin, were caused by the involvement of the cerebellum I am unable to tell. The patient did not undergo

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6. Lhermitte, J., and Klarfeld, B.: Etude anatomique d'un cas d'atrophie croisée du cervelet, Rev. neurol. **22**:73, 1911.

7. (*a*) Cornélius, R.: Les atrophies croisées du cervelet, Thèse de Paris, Paris, Jules Russel, 1907. (*b*) André-Thomas and Cornélius, R.: Un cas d'atrophie croisée du cervelet, Rev. neurol. **15**:197, 1907.

8. Reitsema, J. M.: De indirecte atrophie der kleine hersenen, Psychiat. en Neurol. Bl. **8**:347, 1904; quoted by Cornélius.[7a]

9. Grilis, G. H.: A Case of One Cerebral Hemisphere Supplying Both Sides of the Body, Brit. M. J. **1**:1033 (May 5) 1906.

10. Major, H. C.: Case of Paralytic Idiocy with Right-Sided Hemiplegia; Epilepsy; Atrophy with Sclerosis of the Left Hemisphere of the Cerebrum and of the Right Lobe of the Cerebellum, J. Ment. Sc. **25**:161, 1879.

11. Cramer, A.: Einseitige Kleinhirnatrophie mit leichter Atrophie der gekreuzten Grosshirn-Hemisphäre, Beitr. z. path. Anat. u. z. allg. Path. **11**:38, 1892.

12. Kotschetkowa, quoted by Cornelius.[7a]

13. Mott, F. W., and Tredgold, A. F.: Hemiatrophy of the Brain and Its Results on the Cerebellum, Medulla and Spinal Cord, Brain **23**:239, 1900.

14. Claude, H., and Loyez, M.: Un cas d'atrophie croisée du cervelet, par lésion traumatique de la capsule interne, Encéphale **7**:345, 1912.

a proper neurologic examination, as on both occasions she was in a medical ward because of the grave cardiopulmonic conditions to which she rapidly succumbed.

CONCLUSIONS

1. Crossed atrophy of the cerebellum is a combination of atrophy of a lateral cerebellar lobe with that of the contralateral cerebral hemisphere.

2. The cerebellar changes are similar to those of typical sclerotic atrophy; the cerebral changes vary. They may be cysts, porencephalic or microscopic changes in the form of scattered cell and nerve degeneration of an indefinite etiology.

3. The microscopic cerebral changes may be less intensive than the cerebellar changes but may cover much wider areas, including even the healthy portions of the brain.

4. The changes in the cerebellum are secondary to those of the cerebrum.

DISCUSSION

Dr. William G. Spiller, Philadelphia: In 1901, in the *University of Pennsylvania Medical Bulletin* for June, I reported a case in which internal hydrocephalus was confined to the right cerebral hemisphere, which was a mere sac. Illustrations were published with the report. The left cerebellar hemisphere was much smaller than the right. The primary lesion was evidently the cerebral one and caused atrophy of the opposite cerebellar hemisphere. This was probably one of the earliest reported cases. Since that time several similar cases have been recorded.

Dr. Adolf Meyer, Baltimore: In the late nineties, I had an opportunity to observe and study at autopsy a case of focal paresis in which were present a so-called mind-palsy of one arm and hand and a typical paretic atrophy of the cortex circumscribed in the superior parietal lobule and upper central convolution. There was also a corresponding slight hemiatrophy of the opposite hemisphere of the cerebellum. I am led to speak of it because this interdependence is a regular phenomenon. I had an opportunity to examine the brain by the glia method, and, to my surprise, the whole opposite cerebellar hemisphere showed a marked increase of fibrils, whereas the normal side of the cerebellum did not show that sort of diffuse gliosis. I am sure that the contralateral disturbance in the cerebellum in combination with a cerebral lesion is a typical relation that should receive more attention.

Dr. Edward B. Angell, Rochester, N. Y.: I can contribute another case of the same sort from my experience about 1890, before Dr. Spiller was born—I mean neurologically. A cyst formed during childhood as a result of scarlet fever. The cyst occurred in the arm center of the left side, and the patient lost the use of her right hand. Later in life, she was able to use the left hand only and became competent enough to do satisfactory work in her position in life. Death occurred as a result of a tumor in the pontile region. At autopsy not only was there shrinkage of the brain on the left side but the cortex was much thinned. In the right side of the brain the convolutions were much enlarged, and the cortex

was considerably thickened as compared to the normal, and there was the same contra-atrophy of the cerebellum.

Dr. Wilder Penfield, Montreal, Canada: I think that there is evidence that some of these combined cerebral atrophies and contralateral cerebellar atrophies are not congenital. A case occurred last year, a report of which Dr. Petersen is preparing to publish, in which a head injury produced a subdural hematoma followed by contralateral epileptic seizures and hemiplegia. The patient was a normal child of 3 years at the time of the accident. She died a year later. The hemisphere beneath the hematoma was much smaller than that on the other side. The cerebellar hemisphere opposite the atrophic cerebral hemisphere was much smaller than its mate. On going into the history, it seemed definitely determined that the child was normal before the fall.

Dr. George B. Hassin: The most noteworthy clinical feature of crossed cerebellar atrophy is the possible absence of cerebellar symptoms, regardless of the extent of the atrophy. The symptoms are purely cerebral.

I should like to ask Dr. Spiller whether the case he mentioned is not the same one that he reported with Dr. Wadsworth? Did not Dr. Spiller report some cases in 1896 (in *Brain*) one of which pertained to atrophy of the cerebellum, which I think was also of the crossed type?

Dr. William G. Spiller: I shall have to look it up.

Dr. George B. Hassin: These cases are probably not unusual but are of great biologic interest, for they exhibit, as I said, the predominance of the function of the cerebrum over that of the cerebellum. I also want to emphasize the fact that cerebellar symptoms may be entirely missing even when there is no cerebral atrophy, but not the reverse.

STUDIES IN MULTIPLE SCLEROSIS

IV. "ENCEPHALITIS" AND SCLEROTIC PLAQUES PRODUCED BY VENULAR OBSTRUCTION

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In previous papers it has been shown that a series of histologic pictures resembling those of "postinfectious encephalomyelitis" may be produced in animals by a variety of agents, such as minute doses of tetanus toxin, carbon monoxide poisoning and certain types of embolism.[1] The pathologic alterations ranged, sometimes in a single specimen, from mild perivascular infiltrations with glia and occasional lymphocytic cells through areas of damage to and loss of perivascular myelin to areas of softening and destruction of the axis-cylinders. In one instance, more than a year after the original injection of tetanus toxin, lesions were found which closely simulated those of multiple sclerosis,[2] with plaques of loss of myelin, but with almost complete preservation of the axis-cylinders and with local gliosis. Multiple sclerosis has been observed as a sequel of "postinfectious encephalomyelitis," [3] and the hypothesis that all of these conditions represent variants of the same underlying process seems to gain support from the experiments cited.

The question naturally arises: What common characteristic exists in multiple sclerosis, postvaccinal "encephalitis" and "encephalitis" following measles, the lesions occasionally produced by tetanus and other toxins and the results of carbon monoxide poisoning and embolism? That the lesions of multiple sclerosis are produced by some abnormality of the

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Read before the American Society of Neuropathologists, June 4, 1934.

The expenses of this investigation were defrayed in part by the Harvard Multiple Sclerosis Fund.

From the Neurological Unit, Boston City Hospital, and the Departments of Neuropathology and Surgery, Harvard Medical School.

1. Putnam, T. J.; McKenna, J. B., and Morrison, L. R.: Studies in Multiple Sclerosis: I. The Histogenesis of Experimental Sclerotic Plaques and Their Relation to Multiple Sclerosis, J. A. M. A. **97**:1591 (Nov. 28) 1931.

2. Putnam, T. J.; McKenna, J. B., and Evans, J.: Experimental Multiple Sclerosis in Dogs from Injection of Tetanus Toxin, J. f. Psychol. u. Neurol. **44**: 460, 1932.

3. Kramer, A.: Beginnende multiple Sklerose und akute Myelitis, Arch. f. Psychiat. **19**:667, 1888. Schlesinger, H.: Zur Frage der akuten multiple Sklerose und der Encephalomyelitis disseminata im Kindesalter, Arch. a. d. neurol. Inst. a. d. Wien. Univ. **17**:410, 1909.

blood vessels has been suggested long since (Williamson [4]). Thrombi, chiefly venous, are frequently found in the lesions of "postinfectious encephalomyelitis," [5] including the experimental type, and in the areas of demyelinization of carbon monoxide poisoning. Diffuse demyelinization may be produced by cyanide, an asphyxial poison.[6] On this basis various types of experimental embolism were attempted, but they gave on the whole the least satisfactory imitations of "postinfectious encephalomyelitis," tending to produce areas of complete destruction and cysts of softening. A careful histologic study of the lesions in several cases of multiple sclerosis "postinfectious encephalomyelitis" and of the experimental lesions referred to led to the conviction that if vascular obstruction is the cause of destruction of myelin and proliferation of glia without destruction of the axis-cylinders it must be an obstruction chiefly on the venous side of the capillary bed.

TECHNIC

For a long time, no crucial method for testing this hypothesis presented itself. Finally, the following procedure was devised:

Dogs of various ages were operated on with aseptic precautions, usually being anesthetized with sodium pentobarbital. A button of bone was removed with a trephine from the midline of the cranium, and bleeding was carefully controlled by wax and placement of fragments of muscle. With great care to avoid injury to the arachnoid, the longitudinal sinus was ligated in two places in such a way as to isolate a portion of it into which one or more cortical veins entered. The sinus was pierced with a fine needle, and a mass was injected in such a way as to run backward, upstream, into the cerebral veins, thereby obstructing them (fig. 1). The wound was then closed. The animals were allowed to live for a varying length of time, up to a year, and in all instances were killed by bleeding after being anesthetized with sodium pentobarbital.

HISTOLOGIC RESULTS

Of the fourteen dogs apparently successfully operated on, all but two were found to have cerebral lesions at autopsy. These two were killed relatively late after injection, at ten and eleven months, respectively. It is possible, therefore, that mild changes had been present and had regressed.

The lesions found in the remaining ten animals varied according to the agent used to produce the obstruction, the length of time the animal was allowed to survive and doubtless other factors difficult to analyze.

4. Williamson, W.: Review of the Etiology and Pathology of Multiple Sclerosis, M. Chron. **4**:261, 1903.

5. Kreider, P.: Personal communication to the author concerning work to be published.

6. Ferraro, A.: Experimental Toxic Encephalopathy: Diffuse Sclerosis Following Subcutaneous Injections of Potassium Cyanide, Arch. Neurol. & Psychiat. **29**:1364 (June) 1933.

In one instance a colloidal solution of French shellac was injected, with the result that the animal died on the following day. The dog's brain showed a pathologic picture resembling that of "hemorrhagic encephalitis" which is ascribed to arsphenamine poisoning. In two experiments a sterile suspension of corn-starch was employed, which produced areas of complete softening.

The most satisfactory substances for the purpose in view were found to be various mixtures of oil. Lard oil, which is of course identical with the fat in the animal's own blood, was usually employed, on the grounds

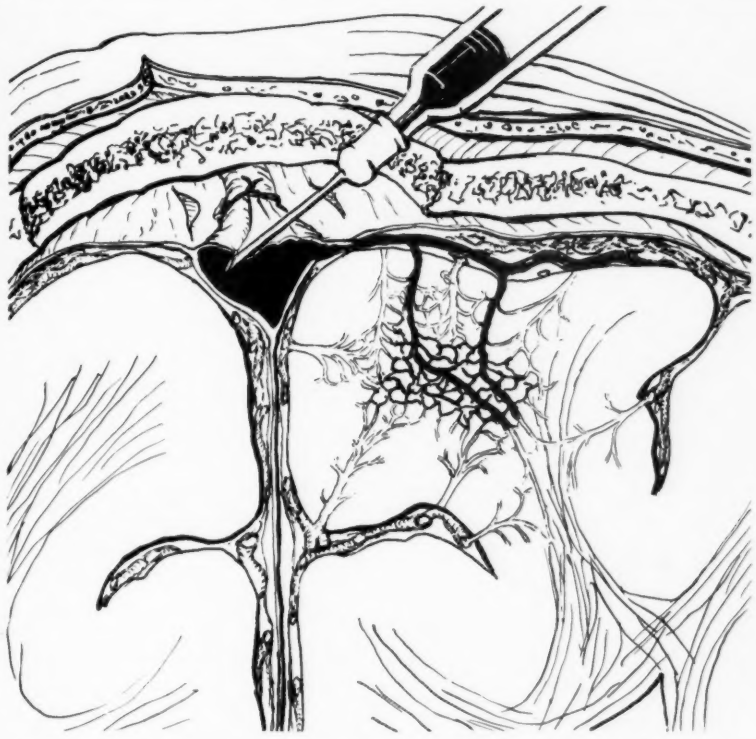

Fig. 1.—A diagram of the experimental procedure, the injection of oil (shown in solid black) into the longitudinal sinus of a dog between ligatures. The oil is forced against the blood stream into the pial and then into the cerebral veins. Perhaps owing to the richer collateral circulation in the cortex, a lesion is produced only in the white matter. Only the venous channels are shown.

that such a bland and physiologic substance could scarcely exert a chemical influence on the vessels or on their surroundings. The only drawback was that when injected under pressure sufficient to force it to the venules it was apt to rupture from smaller vessels and form tiny cysts, chiefly in the border between the cortex and the white matter. Individual droplets of this kind lay inert in the tissue without provoking gliosis or

encystment (fig. 2), but if they occured in groups there were often some actual destruction of the tissue and scarring.

Attention was focused on the successive stages of a characteristic and unmistakable lesion which occurred in various stages of development in ten animals killed at varying intervals of time after the injection of the oil. In five dogs killed at intervals up to four weeks after venous obstruction, a few areas were encountered in the upper parietal and occipital regions in which a diffuse glial proliferation was limited to the

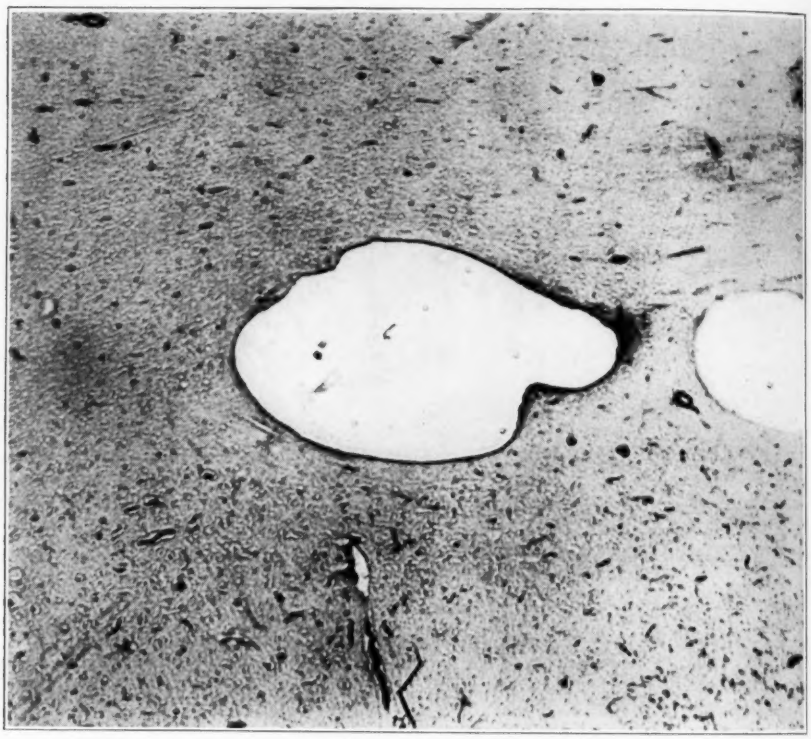

Fig. 2.—Cysts, apparently representing droplets of lard oil are shown lying free in the white matter of the hemisphere ten months after injection into the longitudinal sinus. Note the minimal glial proliferation. Anderson's glia stain; magnification, × 30.

white matter of the convolution containing the obstructed venules (fig. 3). Only one lesion was seen in which the cortex was almost completely destroyed, with little involvement of the underlying white matter (fig. 4). Some of the astrocytes were so swollen that they resembled nerve cells. The formation of fibrils was not striking. There was slight "cuffing" of the obstructed vessels, but the perivascular infiltration was more marked about those still containing blood. The cells in the sheaths

of the vessels were mostly glial, with occasional fat granule cells and rarely cells resembling lymphocytes (fig. 5). The oligodendroglia appeared to be somewhat increased in number. There was no proliferation of the connective tissue. Myelin stains showed some beading and rarely formation of droplets but no definite thinning. Fat stains demonstrated the oil within the vessels and also droplets in the cells about the walls of the vessels. A similar histologic picture, but less intense,

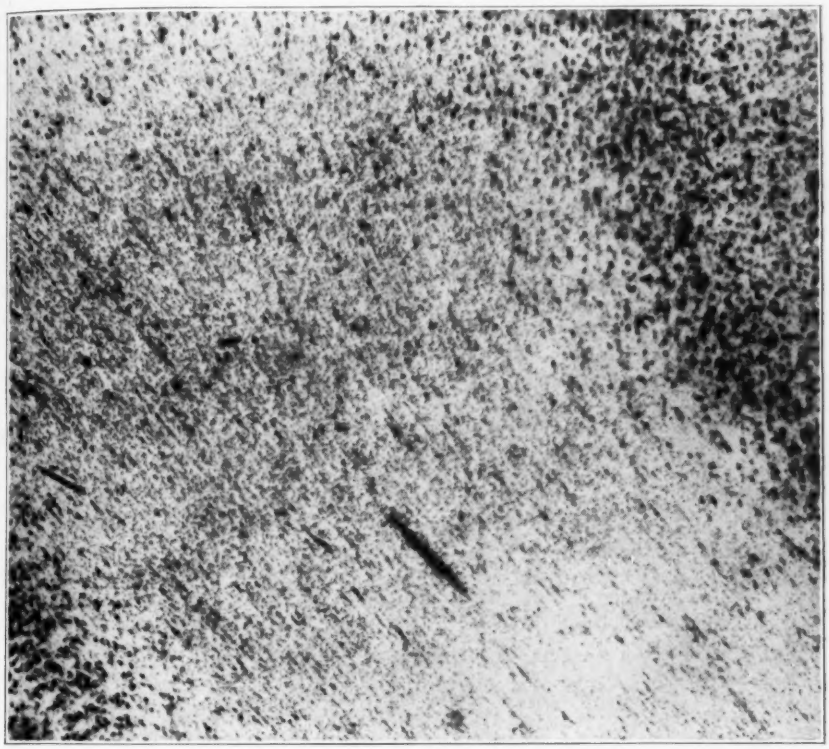

Fig. 3.—The cortex and white matter of a convolution in the hemisphere five days after the obstruction of the venules with lard oil. There is a diffuse glial proliferation largely limited to the deeper portion of the white matter, with mild perivascular infiltration. The cortex shows only minor changes. Cresyl violet stain; magnification, × 30.

was seen in the brains of two other dogs killed six and eleven weeks, respectively, after the operation.

In a dog killed three and a half months after the injection of lard oil into the longitudinal sinus, the most striking changes were those in the myelin. In sections from the upper parietal region, stained by Pal's method, small areas of complete destruction of myelin were seen, while

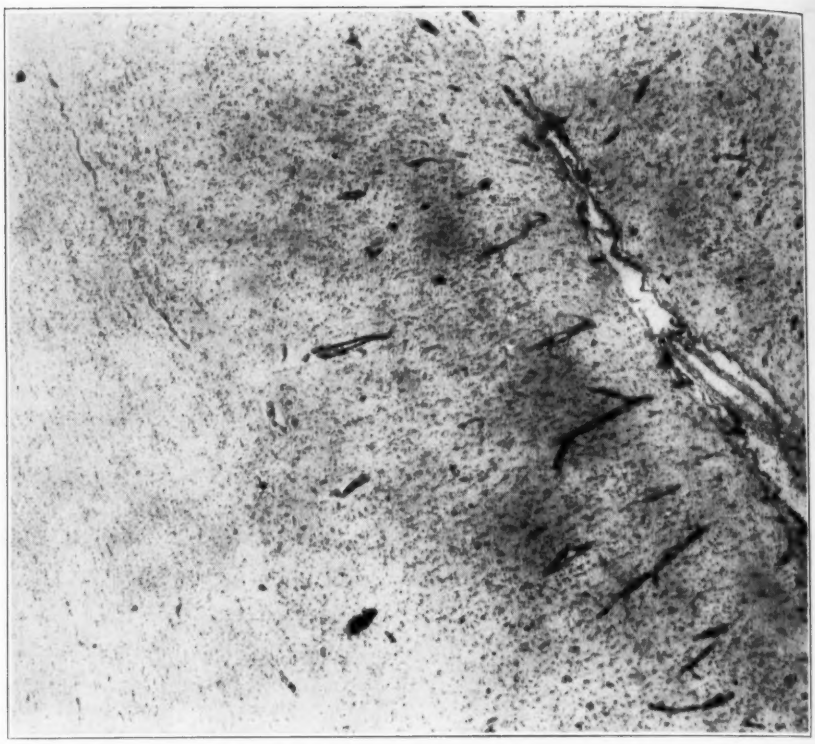

Fig. 4.—The cortex and white matter five days after the injection of lard oil into the longitudinal sinus. In this instance the cortex is chiefly degenerated, and the white matter is relatively intact. Cresyl violet stain; magnification × 30.

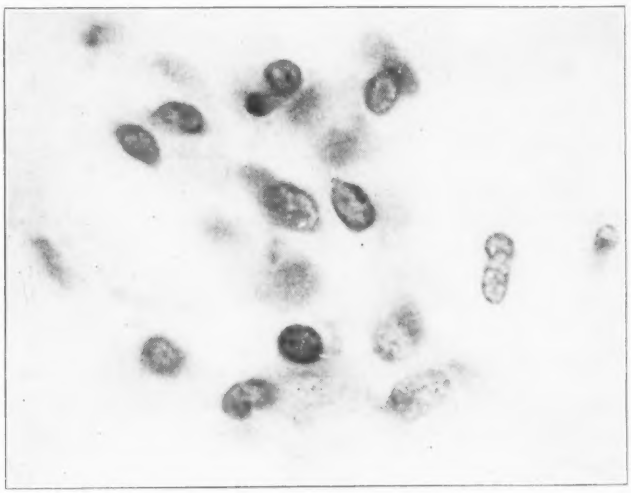

Fig. 5.—A high power magnification (× 500) of one of the cortical vessels in the section shown in figure 3. Infiltration is chiefly by astrocytes and proliferation of fixed glia. Cresyl violet stain.

Fig. 6.—The white matter of the hemisphere of a dog killed three and a half months after the obstruction of the venules with lard oil. The patchy destruction of myelin in some areas is more complete than in others, without loss of the architecture. Weigert-Pal stain; magnification, × 30.

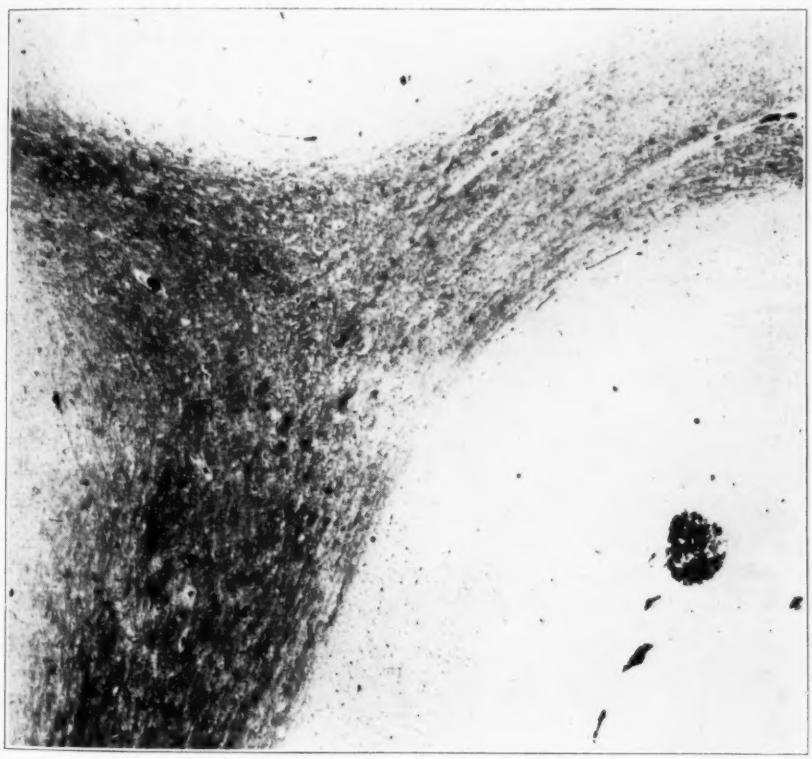

Fig. 7.—A photomicrograph showing the loss of myelin in the tip of an occipital convolution of a dog killed ten months after the obstruction of the venules with lard oil. Weigert-Pal stain; magnification, × 30.

there were marked beading and thinning of the sheaths over a larger, ill defined area (fig. 6). There was far less diffuse cellular increase but more marked perivascular infiltration than in the earlier stage already described. The formation of fibrils had begun but had not produced actual gliosis. The perivascular cells were now all glia and gitter cells, the latter containing droplets of myelin. It was no longer possible to make out which vessels were originally obstructed. The cortex was practically intact. The appearance was that of a "shadow area," such as is often encountered in the cerebral white matter in cases of multiple sclerosis.

A ninth animal was allowed to survive for ten months. Cisternal puncture was performed six weeks after the operation. The cerebro-

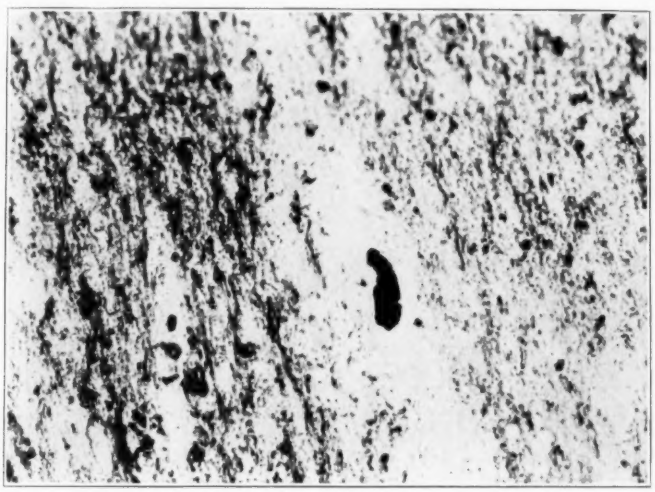

Fig. 8.—A higher magnification (× 300) of part of the denuded area shown in figure 7. Only a few droplets of myelin remain in the field, some of them in phagocytes about a vessel. Weigert-Pal stain.

spinal fluid showed a total protein content of 33 mg. per hundred cubic centimeters, a colloidal gold curve of 0112210000 and 134 lymphocytes per cubic millimeter. The brain appeared to be grossly normal at autopsy ten months after the operation except for one area in which several droplets of fat lay encysted in the gray matter (fig. 2). Independent of this, there was seen in stained sections in the tip of the white matter of one occipital convolution a small area in which only droplets of myelin remained (figs. 7 and 8). They lay mainly in the sheaths of vessels. The edge of the plaque and myelin destruction faded rather gradually into the neighboring white matter in Weigert sections. Anderson's glia stain showed dense gliosis with a moderate cellular increase. The area of gliosis ended sharply at the edge of the white matter and equally

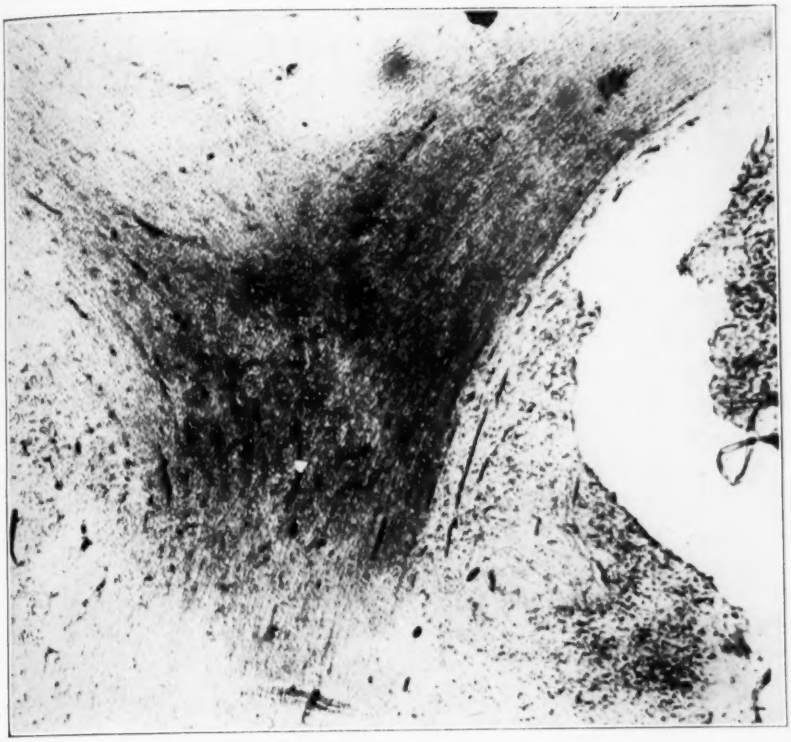

Fig. 9.—A slide from the same block as that shown in figures 7 and 8. Gliosis is sharply limited to the tip of the white matter corresponding to the area of loss of myelin. Anderson's glia stain; magnification, × 30.

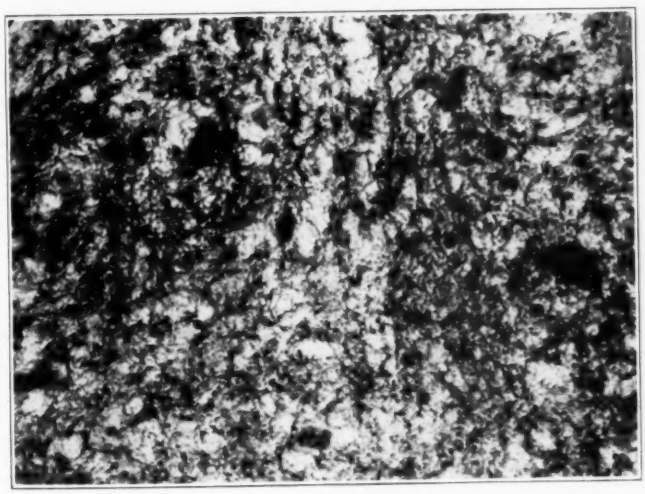

Fig. 10.—A higher magnification (× 300) of the patch of gliosis in the same slide as that shown in figure 9. Anderson's glia stain.

sharply toward the base of the convolution (figs. 9 and 10). Cell stains showed moderate perivascular infiltration, almost exclusively with phagocytic cells. The adventitia of the vessls was somewhat thickened, but there was no evidence of vascular obstruction or proliferation. Davenport's axis-cylinder stain, done on sections taken from the same block as were those just described, showed no appreciable loss of fibers and at the most a slight beading and irregularity (fig. 11). Similar changes, but less intense, were found in the brain of the tenth dog, which was allowed to live for a year after the injection of oil into the longitudinal sinus.

Fig. 11.—A slide from the same block as that shown in figures in the area corresponding to that shown in figure 7. The axis-cylinders are of approximately normal number and are at most slightly swollen and irregular. Davenport's axis-cylinder stain; magnification, × 300.

COMMENT

The results of the experiments reported here are in some respects less dramatic than those reported earlier. The lesions were not disseminated through the spinal cord and optic nerves as in the first animal with "encephalomyelitis" caused by tetanus toxin nor did any of the plaques show as complete demyelinization and as sharp a border as were seen in the second animal reported on in the same paper.[2] Yet in a sense these results are more important than the former ones in that they show unmistakably the chain of events immediately preceding the formation of such a plaque. There can be no question of a specific toxin or virus leaking through the wall of the vessel; the lesion was obviously the

result of a simple mechanical disturbance of circulation which was not severe enough to cause complete necrosis of the tissue.

There can be no doubt also that the earlier stages of the pathologic change produced by venous obstruction must be classed under the general head of "nonsuppurative encephalitis," of which the postinfectious forms may be regarded as especially acute varieties.

The question must inevitably be raised, however, whether even the last stage of the histologic reaction reported here is to be considered identical with the lesions of multiple sclerosis. Certainly it does not reproduce all of them, for, as is well known, a great variety of histologic alterations may be found in that protean disease. It does, however, fulfil the criteria long accepted for the plaques of multiple sclerosis, namely, destruction (but not necessarily complete loss) of myelin, with preservation of the axis-cylinders and localized proliferation of the fibrous glia. If the lesions in question are compared with a series of sclerotic plaques from the cerebral white matter of human beings many of the latter will be found to be similar. To be sure, areas may be found in cases of multiple sclerosis in which there is a denser feltwork of glia fibers, but in the majority of instances there is a more or less complete loss of axis-cylinders in such areas and often there is proliferation of the vessels—in short, there is a mixed scar. A paper on this subject is in preparation. It seems safe therefore to conclude that the experimental lesion closely resembles at least some of the lesions of multiple sclerosis. Moreover, unless one supposes that this peculiar and characteristic histologic complex may be produced by more than one immediately antecedent process, the conclusion appears justified that venous obstruction plays a determinant part in the sequence of events leading to typical sclerotic plaques.

To turn from the strictly histologic to the broader biologic aspects of multiple sclerosis, it appears difficult to conceive of any type of obstruction of the venules except that due to thrombosis, taking into account the clinical as well as the pathologic manifestations of the disease. Venous thrombi have been seen in "postinfectious encephalitis" [5] and in multiple sclerosis.[4] The effect of acute infection and of pregnancy on the course of multiple sclerosis and on the coagulability of the blood is well known. Serologic changes in multiple sclerosis have been reported by Brickner,[7] and work in progress indicates that a specific alteration in clotting may be demonstrable.

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7. Brickner, R.: Studies on the Pathogenesis of Multiple Sclerosis: II. Evidence of the Presence of an Abnormal Lipase in the Blood in Multiple Sclerosis, Bull. Neurol. Inst. New York **1**:105, 1931.

SUMMARY AND CONCLUSIONS

A method is described for producing venous, venular and capillary obstruction with various substances in the brains of dogs.

The histologic changes produced depend on the substance used as an obstructive agent. Several types are briefly described.

By the use of various oils, lesions may be produced which in their early stages closely resemble those of nonsuppurative "encephalitis." It is probable that milder degrees of the reaction may regress in the course of time.

The later stages (up to ten months) of the lesions consist of plaques of demyelinization with practically complete preservation of the axis-cylinders and with dense fibrous gliosis confined to the white matter.

The similarity between such lesions and many of those seen in cases of multiple sclerosis in man is so striking that the conclusion appears almost inevitable that venular obstruction is the essential immediate antecedent to the formation of typical sclerotic plaques.

Certain other facts pointing to the same conclusion are briefly reviewed.

DERMOID TUMORS OF THE SPINAL CORD

REPORT OF FOUR CASES, WITH OBSERVATIONS ON A CLINICAL TEST FOR THE DIFFERENTIATION OF THE SOURCE OF RADICULAR PAINS

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AND
O. W. JONES JR., M.D.
SAN FRANCISCO

Intradural epidermoid and dermoid tumors arising from the conus medullaris and cauda equina are uncommon. In reviewing the reports of large series of cases of tumor of the spinal cord one is impressed by the infrequent occurrence of tumors of this group. In the cases reported in the literature the growths have been classified variously as teratomas, teratoid and epidermoid cysts, cholesteatomas and dermoid tumors, according to the number of germ layers present. According to Ewing's [1] classification teratomas are tumors composed of recognizable tissues and complex organs derived from more than one germ layer. Simple dermoids consist of epidermis, derma and dermal glands, while epidermoid tumors lack definite dermal structures. Tumors of the latter group are usually considered to be of traumatic origin, but certain well defined forms of embryonic derivation are classified as cholesteatomas.

The complex embryologic development of the rectum, anus and caudal end of the spinal cord and its appendages lends itself to the formation of congenital anomalies and of embryologic tumors belonging to this interesting group.[2]

Dermoid tumors of the spinal cord usually occur along the midline from the cephalic to the caudal extremity and not infrequently are associated with congenital anomalies. Cases of embryologic tumor of this type have been reported by various investigators, among them

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From the Department of Surgery, University of California Medical School.

Read at the Sixtieth Annual Meeting of the American Neurological Asso-tion, Atlantic City, N. J., June 6, 1934.

1. Ewing, J.: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1919, p. 931.

2. Keibel, F., and Mall, F. P.: Human Embryology, Philadelphia, J. B. Lippincott Company, 1912, vol. 2. Mallory, F. B.: Sacro-Coccygeal Dimples, Sinuses and Cysts, Am. J. M. Sc. **103**:263, 1892. Streeter, G. L.: Factors Involved in the Formation of the Filum Terminale, Am. J. Anat. **25**:1, 1919.

Fraser,[3] Hosoi,[4] Kubie and Fulton,[5] Gowers,[6] Trachtenberg[7] and Bostroem.[8]

Because of the rarity of such tumors, we report four additional cases of tumor of the cholesteatomatous and dermoid type, all observed within a year.

REPORT OF CASES

Case 1.—M. D., a widow aged 60, was seen first on Feb. 1, 1933. At the age of 18 she had begun to suffer from a "weak back" and from nonradiating pain in the lumbosacral area after exertion. This discomfort continued for twelve years. When she was 30 she had an acute attack of "lumbago" which confined her to bed for three days. Five years later the pain became constant, dull and aching. Roentgen examination at that time revealed spina bifida occulta involving all the sacral segments. During the following twenty years the patient was constantly aware of this pain, but it was not totally incapacitating. At times the pain radiated down the posterior and lateral aspects of the right thigh, and toward the end of this period there developed a slight limp. Thirty-nine years after the onset of the first symptoms she had severe diarrhea, which was controlled with some difficulty. During this illness marked weakness and numbness of the right leg were noted, with aggravation of the usual pain. The patient was unable to walk and had marked muscular spasms in the right leg. There were no disturbances of the sphincters other than urgency after taking cathartics. Because of the spina bifida occulta, the medical attendant advised operation. He reported that there was traction on the dural sac. After the operation the muscular spasms disappeared; otherwise there was no notable improvement. The condition remained nearly stationary for a year, except for the appearance of dull pain in the left lower extremity. At the same time the pain, weakness and numbness increased on the right side. The condition gradually progressed; the patient became unable to walk; the pain became intense, and involuntary contractions of the lower extremities reappeared.

Physical Examination.—On entry, only the following positive findings were detected. Traction on the operative scar did not reproduce the pain. Passive movements of the lower extremities precipitated painful spasms in the hamstring and adductor muscles, which were more marked on the right side. Coarse muscular twitchings were seen in all the muscle groups of the lower extremities. There was complete flaccid paralysis of all the muscles below the right knee, with

3. Fraser, John: A Cystic Dermoid Tumor of the Spinal Cord, Surg., Gynec. & Obst. **51**:162, 1930.

4. Hosoi, K.: Intradural Teratoid Tumors of the Spinal Cord, Arch. Path. **11**:875 (June) 1931.

5. Kubie, L. S., and Fulton, J. F.: A Clinical and Pathological Study of Two Teratomatous Cysts of the Spinal Cord Containing Mucus and Ciliated Cells, Surg., Gynec. & Obst. **47**:207, 1928.

6. Gowers, W. R.: Myo-Lipoma of the Spinal Cord, Tr. Path. Soc. London **27**:19, 1876.

7. Trachtenberg, M. A.: Ein Beitrag zur Lehre von den arachnoidealen Epidermoiden und Dermoiden des Hirns und Rückenmarks, Virchows Arch. f. path. Anat. **15**:274, 1898.

8. Bostroem, E.: Ueber die pialen Epidermoide, Dermoide und Lipome, und duralen Dermoide, Centralbl. f. allg. Path. u. path. Anat. **8**:1, 1897.

such advanced atrophy that the muscles were reduced to fibrous remnants. The right hamstring group was weak. All the muscles in the left lower extremity were acting, but those of the leg and foot were markedly weakened. There was weakness of the gluteal muscles, and the rectal sphincter showed a loss of tone. Complete bilateral anesthesia was present over the areas supplied by the fourth and fifth sacral roots, and there was moderate hypesthesia over the areas supplied by the fourth and fifth lumbar and first and second sacral roots. The patellar and achilles tendon reflexes were absent; there were no pathologic reflexes.

This patient afforded a demonstration of a clinical test by means of which we have found it possible to differentiate radicular pain of intradural origin from extradural pain of radicular type.

Laboratory Examinations.—The blood count, urinalysis and Wassermann test gave negative results.

Roentgen examinations of the lumbar region of the spine showed erosion of the posterior surface of the bodies of the third and fourth lumbar vertebrae, with preservation of the cortex and bilateral thinning of the pedicles of the second, third and fourth lumbar vertebrae.

Lumbar puncture caused intense pain as the spinal needle pressed on the dura. Only a few drops of fluid were obtained. The Queckenstedt test gave evidence of a complete block of the subarachnoid fluid. Two cubic centimeters of iodized poppy-seed oil 40 per cent was injected. Subsequent fluoroscopic examination showed the oil to be stationary but distributed in small drops from the twelfth thoracic to the fifth lumbar vertebra.

Clinical Diagnosis.—On the basis of the clinical findings a diagnosis of tumor of the cauda equina was made.

Operation.—A subperiosteal laminectomy was performed, exposing the dura from the first lumbar to the first sacral vertebra. All the laminae were markedly thinned, and that of the fifth lumbar vertebra was only about 1 mm. in thickness. The dura was in close contact with the ventral surfaces of the laminae, the peridural tissue being absent. The vertebral canal was markedly enlarged and completely filled by a firm, intradural, fusiform mass which extended from the second sacral to the twelfth thoracic vertebrae. When the dura was opened, a yellowish, well encapsulated tumor, measuring 15.2 by 3.8 cm., was seen beneath the arachnoid (fig. 1). At its most caudal point the third and fourth sacral nerves and the filum terminale were displaced to the left. The nerves of the cauda equina were displaced to their respective sides, the tumor occupying a central position in the dural sac. The capsule of the tumor was extremely thin and grayish white. When it was opened yellowish-white cheesy material containing many long and short hairs was found. The entire content was removed; its weight was 45 Gm. The capsule of the tumor was so thin as to resemble leptomeninges and was associated intimately with the roots of the cauda equina. Complete removal was impracticable.

Pathologic Examination.—Gross Observations: The specimen consisted of two parts described as follows: (1) 45 Gm. of a yellowish, fatty, structureless material, which crumbled and broke into small bits, intermingled with many hairs; (2) a small, thin fragment of fibrous-appearing tissue removed from the capsule of the tumor. No cholesterol crystals were found. Some masses revealed evidence of having a cellular structure.

Microscopic Observations: Sections of the largest and most dense masses showed strands of structureless pink-staining fibers which appeared to have held fat. There were small scattered plaques of calcium. A few red blood cells and

leukocytes could be distinguished. The sections from the wall of the cyst showed a thick layer of keratin, on one margin of which was a thinned-out layer of epithelial cells which appeared to have been distorted by pressure (fig. 2).

Diagnosis.—After pathologic examination a diagnosis of dermoid cyst of the spinal cord was made.

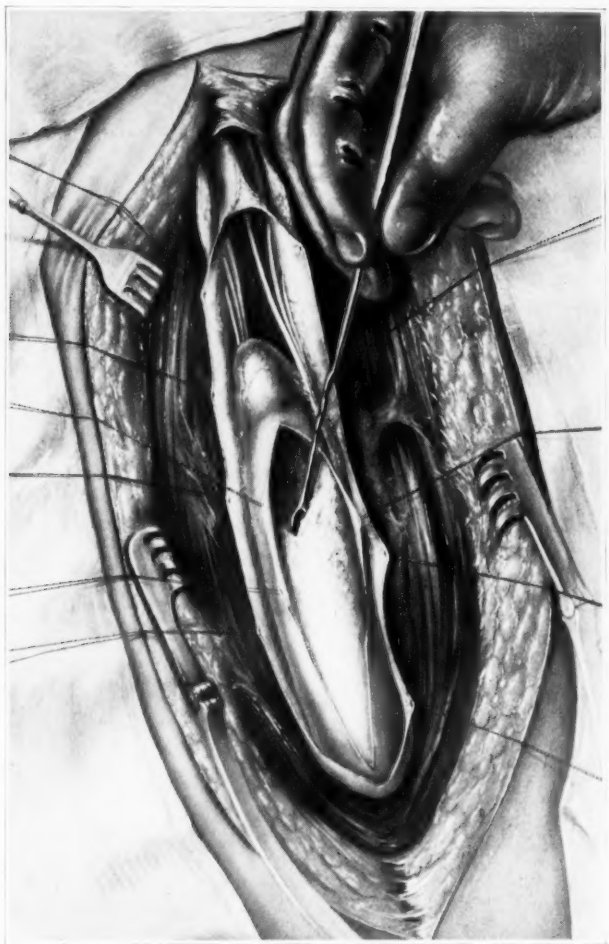

Fig. 1 (case 1).—Drawing made at the time of operation. The capsule of the tumor is open, showing the soft sebaceous content. The roots of the cauda equina can be seen on either side of the tumor.

Course.—The postoperative course was uneventful, and the time of writing (May 1934) the patient was well except for foot drop on the right side.

Case 2.—Mrs. E. S., aged 27, who was seen first on Oct. 4, 1933, had as an initial symptom, two years before, backache low in the lumbar region, with radiation of pain over the distribution of the left sciatic nerve. The course of the

disease was intermittent but progressive. Throughout the entire illness unusually intense pain was the outstanding feature. It gradually increased in severity and intensity, and characteristically started in the region of the third lumbar vertebra and radiated down the posterior aspect of the left thigh into the instep. It gradually spread to the corresponding areas of the right lower extremity. From the onset the pain invariably was aggravated by coughing, straining and sneezing, and during the latter part of the illness, by movements of any part of the body. Urinary frequency appeared four months after the onset of the pain and, after twenty-two months, urinary and rectal incontinence. During these two years endless investigations were made, and treatment for orthopedic and genito-urinary disturbances was instituted. Motor power in the lower extremities was impaired only slightly, but the patient was bedridden because of the extreme pain on movement.

Fig. 2. (case 1).—Photomicrograph showing keratin with a layer of epithelial cells on one margin.

Physical Examination.—The patient was astonishingly emaciated, weighing only 80 pounds (36.3 Kg.), and was in so much pain that the slightest handling or movement was impossible. There was a point of especial tenderness over the spinous process of the third lumbar vertebra. The patient lay in one position and moved the upper extremities only slightly. Other movements aggravated the pain and precipitated painful involuntary muscular spasms in the lower extremities so that it was difficult to evaluate the motor power. All groups of muscles showed proportionate function; no movements were entirely lost. There was no spasticity. There was moderate relaxation of the rectal sphincter. Sensory examination showed an area of anesthesia, about 6.3 cm. in diameter, about the anus but no other sensory alterations. The right patellar reflex was slightly more active than the left; the right achilles tendon reflex was obtained only at times and was sluggish; the left was absent. There were no pathologic reflexes.

This patient afforded an even more striking demonstration of the clinical reaction noted in case 1. The lightest compression of the internal jugular veins reproduced instantly the terrific paroxysms of lumbar and sciatic radicular pain.

Laboratory Examinations.—The blood count and the Wassermann test of the blood gave negative results; the urinalysis showed a faint trace of albumin which, in all probability, was contingent on an existing cystitis.

Lumbar puncture was done under avertin anesthesia. The basal pressure was 100 mm. of water. The response to abdominal pressure was prompt. The

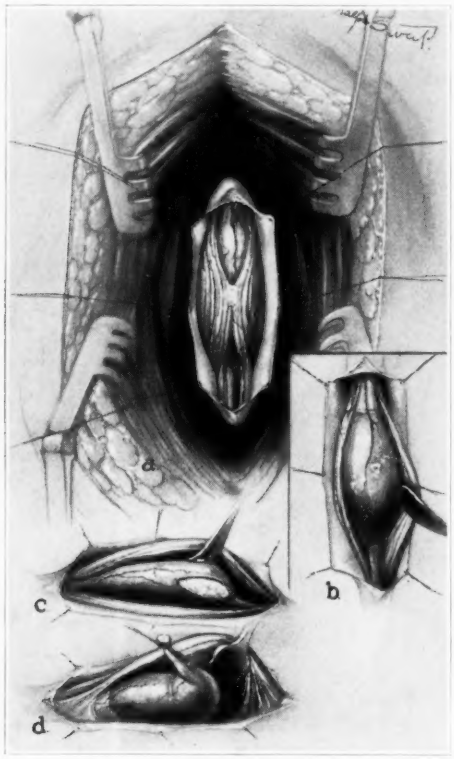

Fig. 3 (case 2).—Drawing made at the time of operation. *a*, indicates the roots of the cauda equina overlying the tumor and adherent at the midline; *b*, the tumor fusing below with the filum terminale and above with the conus medullaris; *c*, the capsule of the tumor open, *d*, the cut end of the filum terminale being elevated with the tumor.

Queckenstedt test demonstrated a complete block of the subarachnoid fluid. The spinal fluid was xanthochromic, and examination showed a marked increase in protein and globulin.

Roentgenograms of the lower thoracic and lumbar regions of the spine showed a widening of the vertebral canal as a result of the thinning of the pedicles of the twelfth thoracic and first and second lumbar vertebrae. There was marked thinning of the lamina of the twelfth thoracic vertebra. The roentgenologic diagnosis

was tumor of the soft tissues of the spinal cord or its membranes, extending from the twelfth thoracic to the third lumbar vertebra and causing pressure erosion of the bony structures of the vertebral canal.

Clinical Diagnosis.—A clinical diagnosis of tumor of the conus medullaris, with compression of the cauda equina was made.

Operation.—By means of a subperiosteal laminectomy the dura was exposed from the twelfth thoracic to the second lumbar vertebra. The dura appeared normal. There was absence of peridural tissue, and the vertebral canal was filled

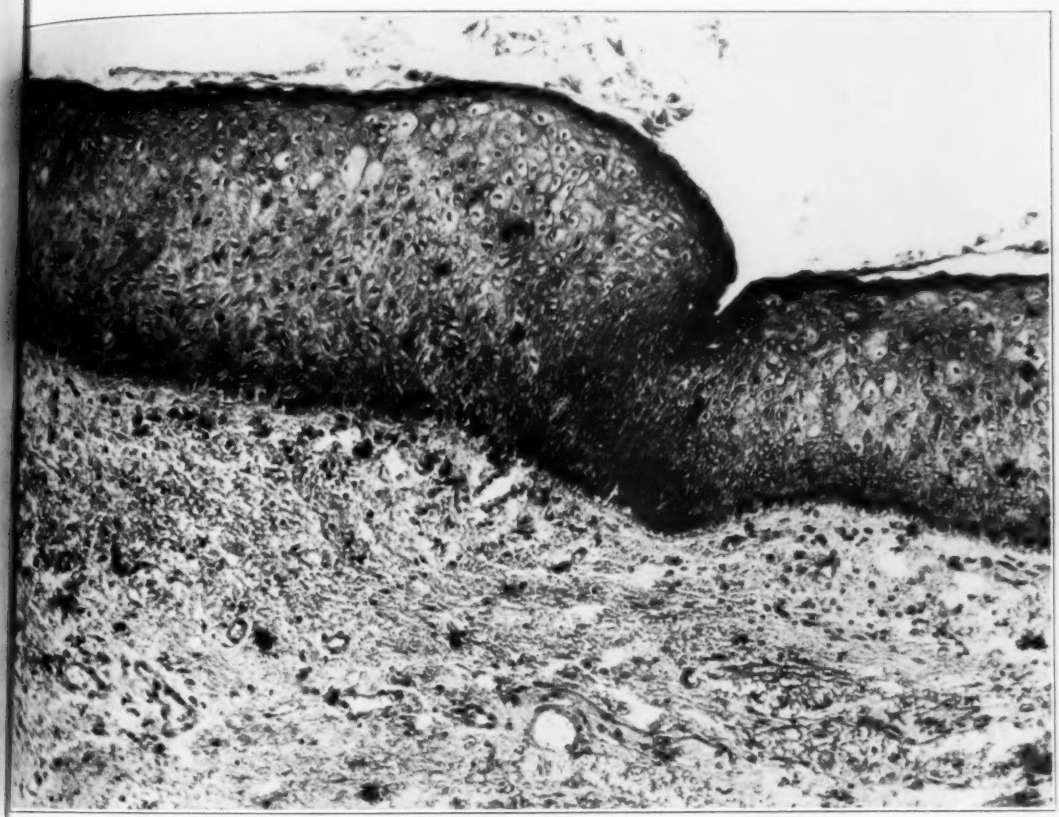

Fig. 4. (case 2).—Photomicrograph showing stratified squamous epithelium.

by the enlarged firm dural sac, which indicated an intradural tumor. When the dura was opened it was seen that the tumor had displaced the roots of the cauda equina dorsally. The lower filaments of the cauda equina arising from the lower half of the conus medullaris were adherent in the midline over the tip of the conus. When these were separated a subpial tumor was seen lying ventral to and to the left of the conus, at which point the two structures were associated so intimately that there was no line of demarcation. Caudally, the tumor tapered into the filum terminale (fig. 3). The encapsulated portion of the tumor was smooth and shiny white. When an opening was made into it, 9 Gm. of white, cheesy material was removed. In order to remove the encapsulated portion of the tumor the filum

terminale was divided. The sac was then elevated and resected where it merged with the conus medullaris.

Pathologic Examination.—Gross Observations: The specimen consisted of approximately 9 Gm. of a grayish-white, structureless, cheesy material that had been broken into many irregular fragments. This material was composed of acellular débris in which were many cholesterol crystals. The specimen also contained two small bits of firm tissue, said to be a part of the capsule enclosing this mass of grumous material. An irregular small mass of firm tissue was included, which

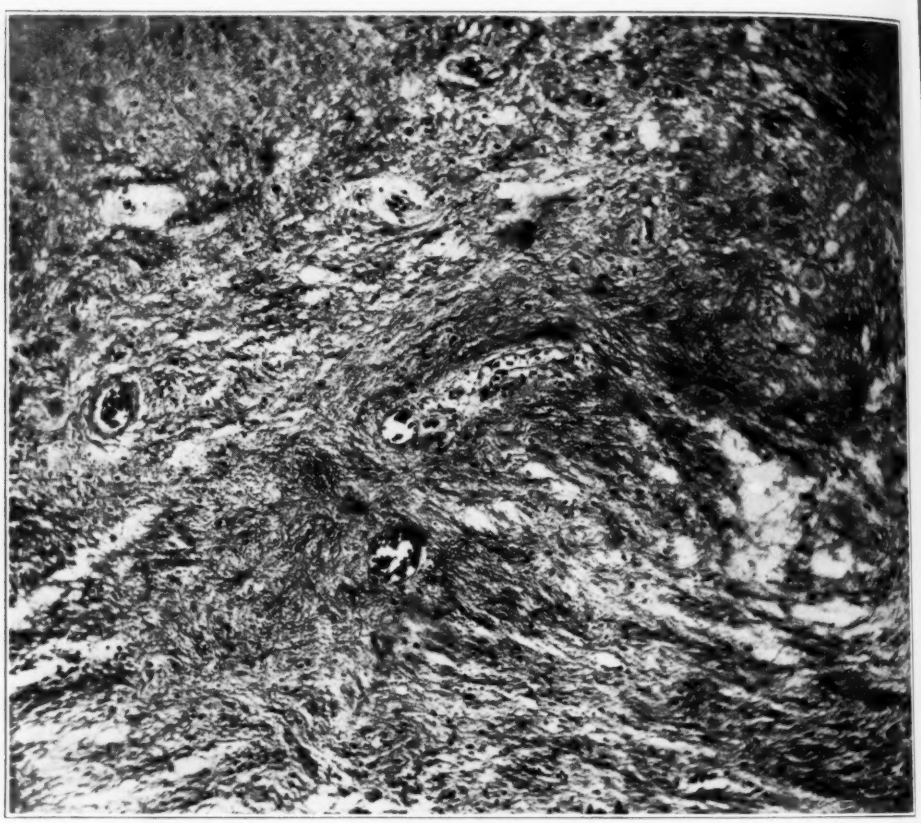

Fig. 5 (case 2).—Photomicrograph showing an area of fibrous astrocytes.

was said to be the filum terminale. It was 3 cm. in length. Attached to it was a portion of tissue which likewise might be capsule.

Microscopic Observations: Preparations of the débris showed it to be composed of degenerated cells, among which were numerous cholesterol crystals. When viewed with the polariscope these crystals revealed the characteristic double refractile property. The capsule showed one border to be lined with stratified squamous epithelium which showed a mild degree of keratinization (fig. 4). Adherent were a few bits of débris. The underlying tissue was composed of a rather avascular, dense, fibroblastic tissue and scar tissue in which were small groups of lymphocytes. There were areas containing fibrous astrocytes. These areas resembled

somewhat the picture seen in a fibrous astrocytoma. Mallory's phosphotungstic acid-hematoxylin stain and Hortega's silver carbonate neurofibril stain demonstrated areas of fibrous astrocytes (fig. 5). Nerve fibers were seen in many areas, especially beneath the capsule. In one region there were two zones of calcium deposition. There were many areas of extravasated red blood cells. The small vessels showed endarteritic changes.

Diagnosis.—A pathologic diagnosis of intradural cholesteatoma of the filum terminale was made.

Course.—The convalescence was uninterrupted. At the time of writing (May 1934) the patient was up and about; she had remained free from pain and had regained control of the sphincters. She was still aware of numbness about the buttocks and perineum as well as down the posterior surfaces of the thighs. A subsequent examination showed that the area of anesthesia about the anus was unchanged. There was hypesthesia over the distribution of the right small sciatic nerve. The left patellar reflex and both achilles tendon reflexes were absent. The motor power in the lower extremities was good.

Case 3.—Mrs. E. G. A., aged 33, was seen first on Sept. 18, 1933. About nine months before admission, for rather ill defined reasons, she had had some chiropractic manipulations of her back. After six of these, dull, burning, constant pain appeared in the posterior aspects of the knees; this pain was aggravated on straining. Soon after, pain occurred in the buttocks, occasionally as high as the sacro-iliac joints, rarely as high as the lower part of the lumbar region of the spine. The pain extended down the posterior aspects of both thighs to the knee on the right and to the ankle on the left; it gradually increased in severity and was aggravated by assuming a sitting position, coughing, sneezing, straining or raising the extended leg. Muscular weakness of the legs gradually appeared, and occasionally there were painful spasms of the legs. There were no subjective sensory alterations or disturbance of the sphincters. During the illness the patient had received various orthopedic treatments, including traction and the application of casts and braces.

Physical Examination.—The results were normal except for a guarding of the lumbar portion of the spine and a slight lumbar lordoscoliosis on the right side. Lateral flexion and rotation of the lower part of the spine were greatly limited. The right leg, extended, could be raised 15 degrees and the left leg 25 degrees before severe steady pain appeared over the sacro-iliac region. Forward flexion of the trunk was slightly limited, but extension was normal. The lower portion of the sacrum was tender to percussion. The patient walked stiffly, with short steps. There were no objective sensory alterations. The achilles tendon reflexes were absent; all others were present and normal. Bilateral jugular compression reproduced the characteristic pain.

Laboratory Examinations.—The blood count, urinalysis and Wassermann test of the blood gave negative results.

Roentgenograms of the lumbar portion of the spine showed normal conditions.

Lumbar puncture was performed through the fourth interspace. Pressure on the dura by the needle caused unusual and severe pain in the left leg. A small amount of fluid was obtained, and the pain was so severe that puncture then was made through the second lumbar interspace. No block of the subarachnoid fluid was demonstrated at that level. The fluid removed from above the tumor showed increased protein and globulin. Two cubic centimeters of iodized poppy-seed oil 40 per cent was injected, and subsequent fluoroscopic examination demonstrated an obstruction at the level of the intervertebral disk between the third

and the fourth lumbar vertebra. After a short delay a few drops of the oil passed to the left of the obstruction and dropped into the caudal sac. The roentgenologic diagnosis was tumor of the cauda equina, almost completely blocking the subarachnoid space.

Clinical Diagnosis.—A clinical diagnosis of tumor of the cauda equina was made.

Operation.—A subperiosteal laminectomy exposed the dura from the second to the fifth lumbar vertebra. The dura appeared normal but when opened revealed

Fig. 6. (case 3).—Drawing made at the time of operation showing the tumor in situ. The insert shows the bed of the tumor after removal.

a white, glistening, encapsulated tumor, about 1.5 cm. in diameter, beneath the arachnoid and resting among the roots of the cauda equina, most of which had been displaced to the right (fig. 6). The dorsal portion of the tumor was free. The capsule was opened, and the content was found to be friable and cheeselike. The capsule and its contents were removed completely except for a small tag of capsule which was adherent to a nerve root.

Pathologic Examination.—Gross observations: The specimen consisted of two separate parts. One was a ball of white, cheesy, structureless material, 1.5 cm. in diameter. This represented the content of the tumor. The remainder of the specimen consisted of three irregular masses of firm pinkish-white tissue

and represented the capsule. The largest piece measured 1.5 by 1.2 by 0.4 cm. in its greatest dimensions. On section the central portion was firm and tendinous.

Microscopic Observations: Sections of the capsule of the tumor showed that it was composed of coarse, compact connective tissue, within which were spaces previously occupied by cholesterol crystals (fig. 7). Along the edges, in several zones, was a blue-staining substance, evidently calcium. Immediately beneath these zones was a layer of cells having small nuclei. The appearance of this layer was suggestive of cartilage (fig. 8). There were scattered areas of round

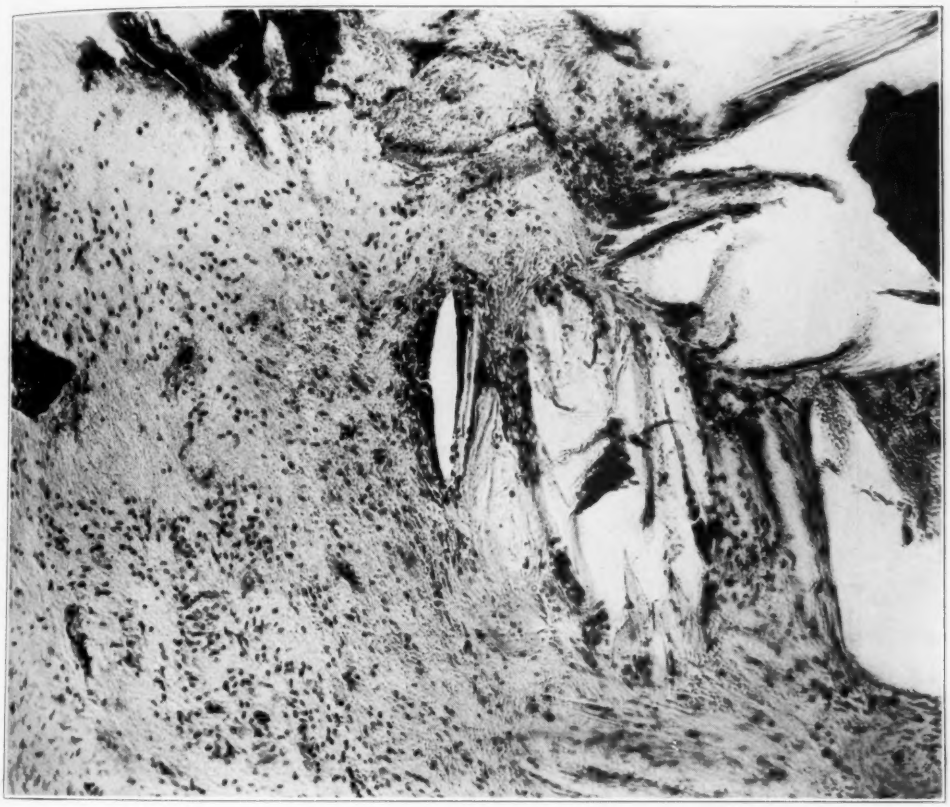

Fig. 7. (case 3).—Photomicrograph showing fibrous connective tissue with cholesterol crystal spaces.

cell infiltration. The white, cheesy substance was composed of empty fat cells and cholesterol crystals.

Diagnosis.—The pathologic diagnosis was intradural cholesteatoma of dermoid origin.

Course.—The convalescence was uneventful, and the patient was relieved completely of the symptoms.

Case 4.—J. M., a man aged 45, was seen first on March 15, 1934. Sixteen years before he had first noted burning, frequency and urgency in urination. At

times he had difficulty in starting the flow, and occasionally he was unable to urinate. Repeated examination gave negative results except for the findings of cystitis and urinary retention. This condition continued for five years, gradually progressing. At the end of that period a calculus of the bladder was removed. Within a month the frequency and urgency became more pronounced, and in addition the patient noted a sense of fulness about the anal region, dribbling of urine and impotence. Six months later numbness of the perineal and perianal regions developed, and the legs became readily fatigued. The condition remained station-

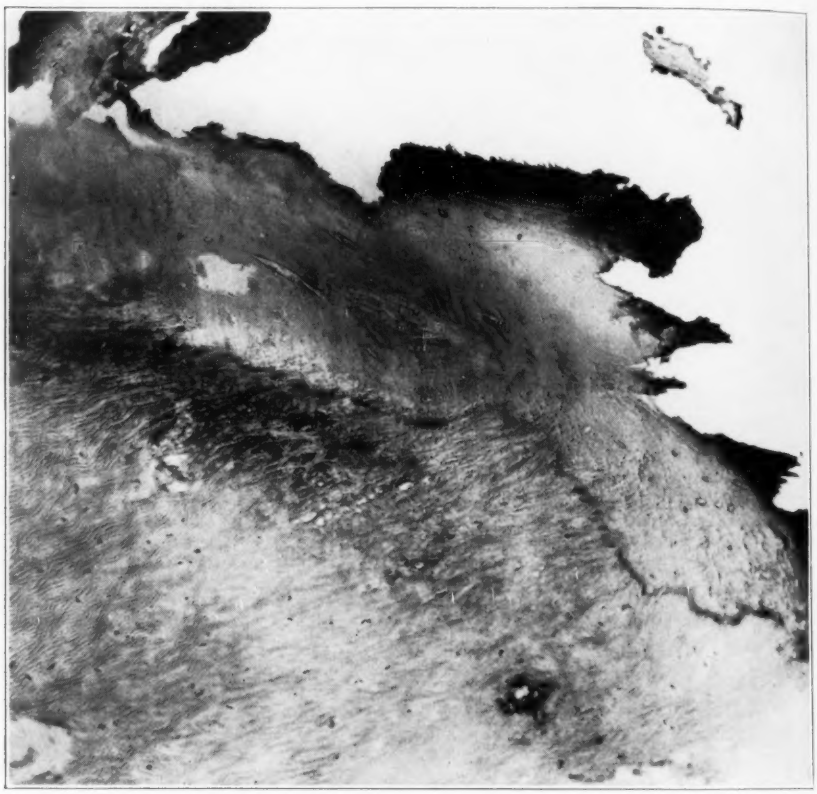

Fig. 8. (case 3).—Photomicrograph showing an area of calcification, a layer of cells resembling cartilage, and fibrous connective tissue.

ary for a year and a half; then the patient became aware of pain which radiated down the posterior aspect of the right lower extremity into the toes. It occurred in paroxysms and was so severe that he was unable to walk. He then became aware of weakness in the right leg and foot, and the numbness progressed down the posterior aspect of the right thigh and the lateral aspect of the leg and over the entire foot. At times he had tingling and numbness down the posterior aspect of the left thigh. Four months prior to his admission to the hospital there developed a constant severe pain down the posterior aspect of the left lower extremity. On coughing, sneezing or straining he had a moderately severe pain about the anus and perineum.

Physical Examination.—On entry the following symptoms were found: Bilateral jugular compression did not reproduce the pain. The muscles of the lower extremities were flabby, and their power was slightly diminished. Dorsiflexion of the right foot was the weakest movement. Coarse fasciculations of the muscles of the thighs and calves were noted. There was complete anesthesia over the area supplied by the first, second, third and fourth sacral nerves. The right patellar reflex was slightly more active than the left; both achilles reflexes were absent; the cremasteric reflexes were active and equal. There were no pathologic reflexes.

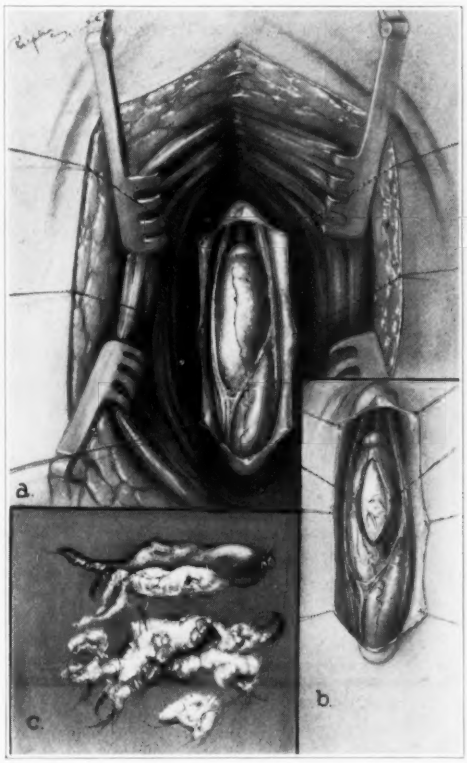

Fig. 9. (case 4).—Drawing made at the time of operation: *a* indicates the tumor, showing fusion with the filum terminale and relationship to the conus medullaris; *b*, capsule of the tumor, open; *c*, the tumor after partial removal (the cheesy contents contain hair; there is a silk ligature on the cut end of the filum terminale).

Laboratory Examinations.—The blood count and Wassermann test of the blood gave negative results; the urinalysis showed definite evidence of urinary infection.

Roentgenograms of the thoracic, lumbar and sacral regions of the spine showed no abnormalities.

Lumbar Puncture: The spinal fluid was clear; the basal pressure was 150 mm. of water; the abdominal responses were normal. Bilateral jugular com-

pression showed no evidence of a block of the subarachnoid fluid. Two cubic centimeters of iodized poppy-seed oil 40 per cent was injected, and subsequent fluoroscopic examination showed that the oil passed rapidly up to the level of the first lumbar interspace, where it was obstructed. After a short time it passed along the right side of the dural sac. The roentgenologic diagnosis was subdural tumor at the level of the body of the first lumbar vertebra. Examination of the

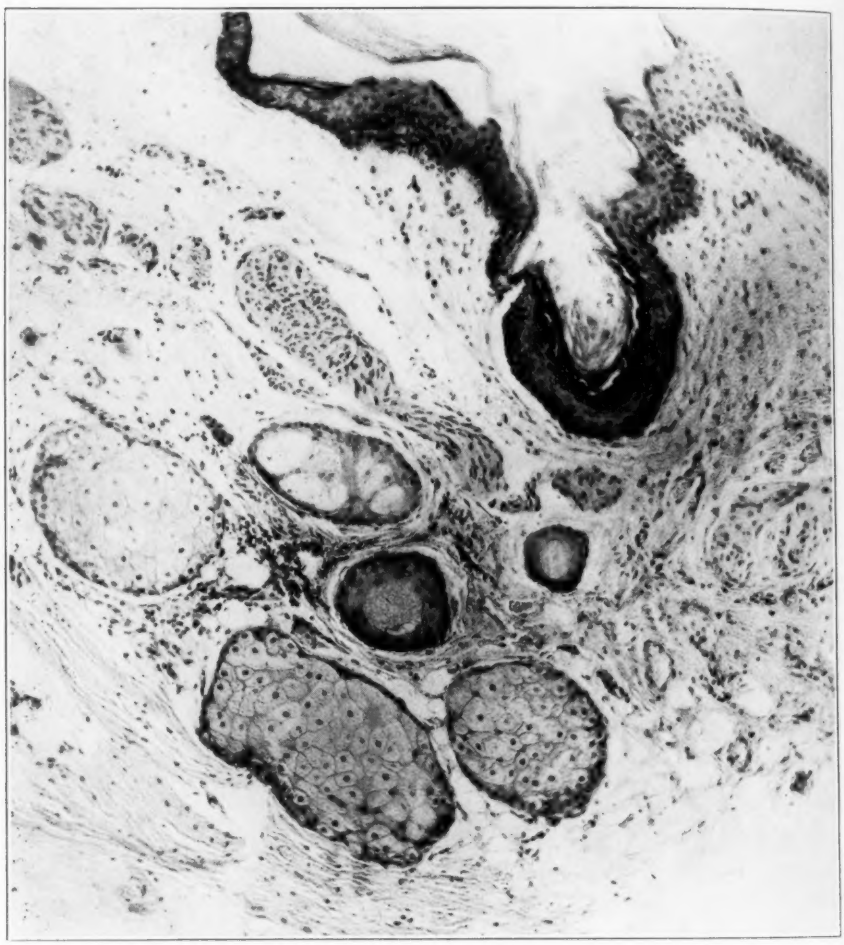

Fig. 10. (case 4).—Photomicrograph showing hyperkeratotic stratified squamous epithelium and sebaceous glands.

spinal fluid gave negative results except for a marked increase in the amount of protein and globulin.

Clinical Diagnosis.—The clinical diagnosis was dermoid tumor of the cauda equina.

Operation.—A subperiosteal laminectomy exposed the dura from the eleventh thoracic to the third lumbar vertebra. The dura appeared normal, but palpation

revealed an underlying firm mass. On opening the dura a subpial tumor was exposed, which measured 5.5 cm. in length and completely filled the dural sac. The tumor had displaced the conus medullaris and the roots of the cauda equina to the left (fig. 9). In its lower half it was definitely encapsulated but tapered down and blended with the filum terminale from which it appeared to arise. Proximally there was no line of demarcation between the tumor and the conus

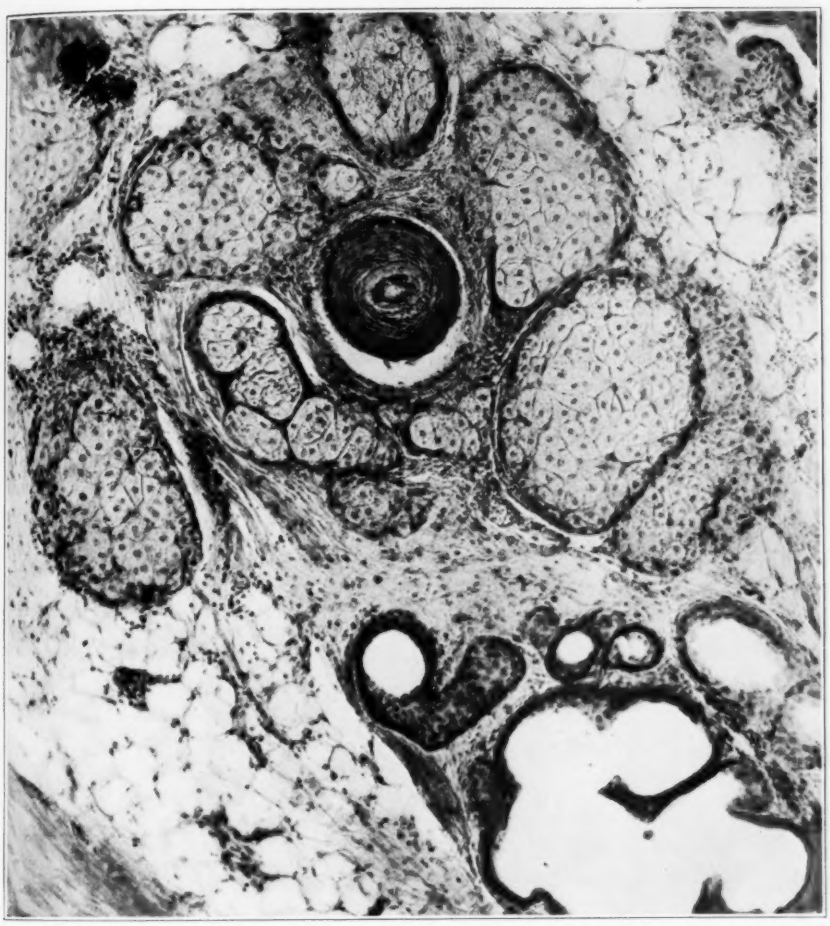

Fig. 11. (case 4).—Photomicrograph showing hair follicles, sebaceous glands and sweat glands.

medullaris. At a distance of about 2 cm. below the point at which the tumor tapered into the filum terminale the latter was divided. When the capsule of the tumor was opened it was found to contain white, cheesy material in which were many long and short hairs. Following the removal of the contents of the tumor, the capsule, which was associated intimately with the roots of the cauda equina, was dissected free to the point at which it blended with the conus medullaris, where it was divided. Palpation of the conus medullaris showed it to be firmer

than normal. At the point at which the tumor blended into the filum terminale the tissue was firm and dark blue and appeared to represent the active portion of the tumor.

Pathologic Report.—Gross Observations: The specimen consisted of a conical piece of firm tissue, the outer surface of which had a definite smooth capsule. The smaller end of the mass was 1.5 mm. in diameter and represented the cut end of the film terminale. The largest diameter was 1.4 cm. On the inner surface of the conical mass was a cavity lined with a smooth, shining membrane. On sectioning through the mass, calcified areas were encountered. The cut surface was gelatinous and dull gray. Many small areas of calcification were seen. Fibrous-appearing strands of varied thickness divided the tumor into irregular areas. There were many small cystic areas of degeneration. The capsule of the tumor could not be peeled away. Several small pieces of white caseous material contained many long and short hairs.

Microscopic Observations: The outer surface of the capsule consisted of a thin layer of connective tissue. Immediately beneath this layer were several large and small nerve bundles. The inner surface of the capsule was lined with a hyperkeratotic, stratified, squamous epithelium (fig. 10). Beneath the epithelium, in loose connective tissue, were scattered hair follicles, sebaceous and sweat glands (fig. 11) and normal fat cells. A few spicules of bone and calcium granules were seen. There were scattered areas made up of small lymphocytes and polymorphonuclear cells. Mallory's phosphotungstic acid-hematoxylin stain and Hortega's silver carbonate neurofibril stain showed areas of fibrous astrocytes.

Diagnosis.—A pathologic diagnosis of intradural dermoid cyst of the filum terminale was made.

Course.— At the time of writing the patient was convalescing satisfactorily and had been relieved of pain. It was, however, too early to judge the outcome.

COMMENT

We wish to call attention particularly to a clinical test which has enabled us to differentiate radicular pain of intradural origin from extradural pain of radicular type. In cases of gross space-consuming lesions within the spinal canal, radicular pain commonly is caused by tension or traction on sensory roots. In lesions of the cauda equina, pain, particularly of the bilateral sciatic type produced by coughing, straining, sneezing or muscular movements, has long been known to be characteristic. It is well known, however, that muscular movements, straining or any sudden effort, such as coughing or sneezing, may give rise to pain in patients with sciatica resulting from lumbosacral, sacro-iliac and other lesions of extradural origin.

The test is performed readily in the office or on a patient confined to bed; the method is as follows: The patient is placed in a comfortable position, and when he is free from pain the cervical veins are compressed as in the familiar Queckenstedt test. As the intracranial and intraspinal pressure above the level of a block is raised the typical radicular pain is reproduced because the tumor or other gross lesion presumably is displaced sufficiently to cause traction on or irritation of a nerve root.

Although the radicular pain most often is reproduced on compression of the jugular and other cervical veins, in certain instances, depending presumably on the direction in which the tumor dislocates most readily, such pain may be experienced only on the sudden release of the jugular compression.

Though radicular pain is more common in cases of tumor of the cauda equina, the value of the test is by no means limited to tumors of that region but is of differential value also for lesions at all levels, and radicular pain has been produced in the same manner in cases of tumor of the cervical and thoracic regions. It is easy to understand the dislocation of a pedunculated neurofibroma with its traction on a sensory root occurring as a result of this test, but in addition the test was found to be positive in association with other gross lesions, such as spongioblastoma multiforme of the conus medullaris, hemangio-endothelioma involving the cauda equina and conus medullaris, and arachnitis serosa circumscripta of the fourth thoracic segment, as well as in three of the four cases reported here.

It may be said that if the test is positive it furnishes presumptive evidence of the presence of a gross, space-consuming intradural lesion. On the other hand, a positive reaction may not be obtained in all persons with tumor of the spinal cord. The test, however, is positive so frequently in such cases and is so reliable that we recommend it as a definite diagnostic aid.

Viets,[9] in 1928, suggested that if a lumbar puncture was performed below the level of the block in a case of tumor of the cauda equina and the fluid drained from below the block, jugular compression might reproduce intense pain in the segmental area corresponding to the uppermost root affected by the tumor. Our experience, under these circumstances, has been similar.

Another sign of diagnostic value was present in two of the four cases reported. In cases 1 and 3, when the needle encountered dural resistance at the time of lumbar puncture, the patient experienced excruciating pain. In case 3 the fluid was obtained on puncturing in another interspace, but in case 1, regardless of the interspace used, pain was so intense that it was necessary to employ general anesthesia in order to complete the puncture. At operation the condition found readily explained the cause of the pain. In each instance a tumor was found anterior to the roots of the cauda equina, displacing the roots posteriorly against the dura so that they were immobile and under tension. The slightest pressure on the dura irritated the immobile nerve roots, causing pain. In a suspected case of tumor, therefore, severe

9. Viets, H. R.: Two New Signs Suggestive of Cauda Equina Tumor: Root Pain on Jugular Compression and Shifting of the Lipiodol Shadow on Change of Posture, New England J. Med. **198**:671, 1928.

pain produced during a lumbar puncture is suggestive. Careful examination of the end of the needle should be made for fragments of tissue. In some instances such fragments may not only confirm the diagnosis but reveal the pathologic type of the tumor.[10]

Primary tumors of the spinal cord, spinal roots and their membranes frequently cause secondary bony changes which are demonstrable roentgenographically.[11] In two of the cases here reported the slow-growing nature of the tumor produced definite bony alterations which were demonstrated by roentgen rays. These alterations consisted in narrowing of the pedicles, thinning of the laminae and erosion of the posterior surfaces of the bodies of the vertebrae, with resulting enlargement of the vertebral canal. A recent article by Camp, Adson and Shugrue[12] described the various bony changes found in association with tumors arising from the spinal cord and its meninges, as demonstrated by roentgen rays. Their opinion was that bony changes can be demonstrated in from 15 to 20 per cent of cases in which tumors arise from the tissues within the spinal canal and that the changes are frequently characteristic of the underlying lesion.

SUMMARY AND CONCLUSIONS

1. Intradural, epidermoid and dermoid tumors of the filum terminale, conus medullaris and cauda equina are uncommon.

2. Four cases of this type of tumor are reported, three of which occurred in women. In two cases the long duration of the symptoms is notable—forty-two years in one instance. In only one case was there an associated congenital bony anomaly.

3. Bony changes in the neural arch, as demonstrated by roentgen examination, are frequently found in association with slow-growing tumors.

4. The production of severe pain on lumbar puncture may be indicative of a gross lesion of the cauda equina, as demonstrated in cases 1 and 3.

5. The clinical test of reproduction of typical pain on jugular compression, as described, is recommended as a diagnostic aid in differentiating radicular pain produced by gross intradural space-consuming lesions from extradural pain of radicular type.

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10. Parker, H. L.: The Diagnosis of Tumors of the Cauda Equina, Conus and Epiconus Medullaris; Report of Nine Cases, Am. J. M. Sc. **163**:342, 1922. Collins, J., and Elsberg, C. A.: Giant Tumors of the Conus and Cauda Equina. Am. J. M. Sc. **147**:493, 1914. Kubie and Fulton.[5]

11. Elsberg, C. A., and Constable, K.: Tumors of the Cauda Equina: Differential Diagnosis Between New Growths and Inflammatory Lesions of the Caudal Roots, Arch. Neurol. & Psychiat. **23**:79 (Jan.) 1930.

12. Camp, J. D., Adson, A. W., and Shugrue, J. J.: Roentgenographic Findings Associated with Tumors of the Spinal Column, Spinal Cord and Associated Tissue, Am. J. Cancer **17**:348, 1933.

PARENCHYMATOUS CORTICAL CEREBELLAR ATROPHY (SUBACUTE CEREBELLAR ENCEPHALITIS)

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Knowledge regarding various types of atrophy of the cerebellum is still sadly incomplete. An attempt was made in a previous contribution [1] to bring up to date a report on the literature describing a particular type of atrophy, and the clinical and pathologic details of one new case were described. At that time it seemed as if there was a certain degree of uniformity in the descriptions of the disease; more careful scrutiny of the reported cases, however, suggested the advisability of further divisions in the classification. Accordingly, in view of this, and considering the scanty knowledge of the subject, we thought it worth while to review this type of atrophy once more, especially in the light of our recent experience.

Parenchymatous cortical cerebellar atrophy is a rare disease. We were able to find only twelve well authenticated cases reported in the literature wherein both clinical and pathologic details were reasonably complete. The disease occurs more frequently in men past middle age or in the sixth and seventh decades of life. Of insidious onset, it progresses slowly toward complete helplessness and death from some intercurrent disease. As might be anticipated, the dominant complaint is in reference to equilibrium, and all the patients have difficulty in walking because of ataxia of the cerebellar type. The lower extremities are involved first and in a symmetrical fashion, so that the gait becomes hesitating and swaying with oscillations in the anteroposterior direction. The legs are spread widely apart for more firm support; in time a cane has to be used, to be discarded later for crutches; finally, the patient becomes unable to walk at all. The upper extremities may escape entirely; if they do become affected it is later in the course of the disease and seldom to the same extent as the legs. Handwriting may become illegible; food is spilled on the way to the mouth, and finer coordinated

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Read at the Sixtieth Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 5, 1934.

1. Parker, H. L., and Kernohan, J. W.: Parenchymatous Cortical Cerebellar Atrophy (Chronic Atrophy of Purkinje's Cells), Brain **56**:191 (July) 1933.

movements become impossible. Dyssynergia, dysmetria and dysdiadokokinesis are companion features to disturbance of equilibrium. In a relatively small number of cases there is an element of spasticity in the lower extremities, and speech is usually described as being monotonous, drawling, slow, staccato or explosive. Nystagmus is not a prominent feature. Intelligence is preserved, and there is no pain or suffering.

Pathologic changes in the cerebellum in the majority of cases are revealed grossly by atrophy of such extent that the cerebellum is reduced by a third or a fifth. To this, however, there have been notable exceptions, and in at least three of the twelve cases the cerebellum disclosed no alterations on gross examination. In cases of atrophy there are widening of the sulci and both shrinkage and hardening of the folia; the degree of these changes is most marked in the anterior portion of the superior vermis and in the middle portion of the quadrilateral lobule.

In microscopic sections which have been stained suitably, the outstanding feature is the total or nearly total disappearance of the Purkinje cells with, however, preservation of the baskets. On this fundamental point, all investigators are agreed. In cases of marked atrophy the breadth of the granular and molecular layers is diminished. These layers stain less intensely, but there is no gross alteration in their architecture and no extensive destruction of any cells other than Purkinje cells. In some instances the white matter of the folia is sclerosed, and where it joins the white matter of the central portion of the cerebellum there is a distinct margin. The dentate and other roof nuclei are uninjured, and the climbing fibers, mossy fibers and T-shaped fibers remain intact. Changes do not appear in the white matter of the central portion of the cerebellum. In some cases, but not in all, there are atrophy and sclerosis of the posterior median portion of the inferior olivary nucleus, and its connecting cerebello-olivary tracts may be degenerated in part. Marie, Foix and Alajouanine[2] insisted that Purkinje cells in the superior vermis and quadrilateral lobule are affected most; they drew certain conclusions therefrom. In our case the reverse held true, in that the only normal Purkinje cells were found in the superior vermis. According to other observers, there seems to be no uniformity in the distribution of injured tissue; the meninges were thickened, as likewise was the intima of the blood vessels in a case described by Archambault,[3] but this is the only example of such a

2. Marie, Pierre; Foix, C., and Alajouanine, T.: De l'atrophie cérébelleuse tardive a prédominance corticale, Rev. neurol. **38**:849 (July); 1082 (Aug.) 1922.

3. Archambault, La Salle: Parenchymatous Atrophy of the Cerebellum, J. Nerv. & Ment. Dis. **48**:273 (Oct.) 1918.

condition and in the other cases described all evidence of inflammatory processes, old or new, was lacking. In our case diffuse pigmentary changes were present in all the larger ganglion cells of the central nervous system, but again this was the only recorded instance of such changes, and it is consequently of doubtful significance. In sum, therefore, the disease consists of chronic progressive disturbance of equilibrium, with or without incoordination of the upper extremities, and at death there is total or nearly total absence of Purkinje cells with preservation of the basket cells; there are few pathologic changes other than this.

So far, the uniformity of opinion regarding the disease has been disturbed only by minor factors. Very serious discrepancies and differences of opinion arise, however, when the etiology of the disease is discussed. Further, the rapidity of its course differs too widely in some instances to be set aside as a minor variation in the average course of the disease. The idea that different factors in the etiology of this disease are responsible for the variability in its rate of progress at once comes to mind. Murri's [4] patient had severe gastro-enteritis throughout the disease, which ran its course in the relatively short period of eight months. By contrast, Lhermitte's [5] patient suffered from no infectious episode and lived thirteen years, dying of carcinoma of the pancreas, obviously an intercurrent disease. Our patient succumbed within two years to carcinoma of the ovary, but cerebellar ataxia had progressed to an extreme degree six months before. Archambault's patient had a severe illness characterized by gastro-intestinal disturbance and fever at the age of 17. Thereafter, he was clumsy and awkward and showed muscular incoordination, but no progression occurred until the age of 40, when he became gradually worse; he died, ataxic and helpless, at 65. It is no wonder, therefore, that various etiologic possibilities present themselves.

Marie, Foix and Alajouanine emphasized two main factors: an early infectious process antedating the appearance of the disease and the onset of the disease late in the life of the patient. They suggested that a previous infectious or toxic condition impairs a poorly endowed Purkinje cell system, leading later to premature decay—in other words, a double pathogenesis. Archambault also pointed out the possibility of an early infectious process affecting the meninges and blood vessels and leading to progressive atresia of the latter, so that in later life there appears progressive cortical atrophy from malnutrition. Stender

4. Murri, A.: Degenerazione cerebellare da enterogena, Riv. crit. di clin. med. **1**:593 and 609, 1900.

5. Lhermitte, J.: L'astasie-abasie cérébelleuse par atrophie vermienne chez le vieillard, Rev. neurol. **34**:313, 1922.

and Lüthy's [6] patient suffered from alcoholism, and after his third bout of delirium tremens a progressive cerebellar syndrome developed. Ferraro and Hernandez [7] demonstrated by experimental work that lead may injure the Purkinje cells but that other cells are affected equally. Jelgersma's [8] patient had never had an antecedent illness when, at the age of 80, he became afflicted with ataxia; he did not die, however, until eight years later. In accord with the work of Ellis,[9] who found a gradual loss of Purkinje cells with advancing age, one might assume the possibility of senile abiotrophy among patients of more advanced age. In the final analysis there probably is more than one etiologic factor.

Attention has been drawn to the possibility of a virus disease with a special affinity for the Purkinje cells which attacks younger patients, runs a much more rapid course and is associated with general weakness and prostration. This disease shows certain analogies to chronic anterior poliomyelitis, to Parkinson's syndrome of epidemic encephalitis and to the disease known as "louping ill" in animals. The case of Murri and that previously reported by us may fall into this category; the following case suggests even more strongly the possibility of a virus infection.

REPORT OF A CASE

History.—A hardware merchant, aged 49, came to the Mayo Clinic on Jan. 9, 1934, with the complaint of weakness and unsteady gait. His mother died of senility at the age of 82, and his father died of renal disease at the age of 68. One brother was killed in an accident; four sisters were living and well. None of his known relatives had had a disease similar to his. He was married and had two children who were living and well. He had had few illnesses in his life. He said that he had typhoid twenty-eight years before but that it was not severe and left no residue. He also had a slight attack of influenza fifteen years previously, but this did not necessitate his being confined to bed. He was not addicted to the use of alcohol or drugs, and there was no known source of contact with poisonous materials. For several years he had intermittent attacks of abdominal distress about two hours after meals which were relieved by sodium bicarbonate; these attacks never incapacitated him. Twelve months prior to admission he noted marked loss of appetite and began to lose strength and weight rather rapidly, so that he lost on the average over 2 pounds (0.9 Kg.) a week. An insidiously developing ataxia was associated with this weakness, so that he would have swayed to the right or left when walking unless he had been very watchful. He tired more easily. His color became sallow, and within nine months he lost about 80 pounds (36.3 Kg.). All these complaints progressed steadily up to the time of

6. Stender, Arist, and Lüthy, Fritz: Ueber Spätatrophie der Kleinhirnrinde bei chronischem Alkoholismus, Deutsche Ztschr. f. Nervenh. **119**:604, 1931.

7. Ferraro, A., and Hernandez, R.: Lead Poisoning, Psychiatric Quart. **6**:121 (Jan.); 319 (April) 1932.

8. Jelgersma, G.: Eine Systemerkrankung in Kleinhirn, J. f. Psychol. u. Neurol. **25**:42, 1919.

9. Ellis, R. S.: Norms for Some Structural Changes in the Human Cerebellum from Birth to Old Age, J. Comp. Neurol. **32**:1 (Aug.) 1920.

examination. Six months previously he was in an automobile accident, but he was not severely hurt, although thereafter he noticed that in walking he tended to pitch forward and later he had to use a cane to get around. Four months previously vomiting after meals appeared; this vomiting was projectile, forcible and without nausea or warning. He also complained of diplopia and photophobia. Three months before examination his hands became unsteady, so that his writing became more and more illegible; he also had difficulty in dressing himself or in tying packages. His gait by this time was such that even with a cane he staggered conspicuously and preferred to hold some person's arm in going through the streets. One month before admission the weakness and ataxia reached such a stage that he remained in bed, and there was such increasing drowsiness that he slept at all hours of the day; however, he was perfectly rational when awake. Appetite improved at that time and he ceased to lose weight, but he had increasing constipation. Examination of the spinal fluid elsewhere had revealed a negative Wassermann reaction, and the fluid was clear. He had no headache and was normal mentally.

Examination.—The patient looked ill and weak because of his sallow color and obvious signs of loss of weight. He appeared for examination in a wheel-chair, although he could still walk short distances with the aid of a cane and with his wife's support. The systolic blood pressure in millimeters of mercury was 106 and the diastolic 94. Vision with correction by lenses was 6/6 in the right eye and 6/7 in the left. The pupils were irregular but reacted normally. No abnormal changes were found by ophthalmoscopic examination of the ocular fundi. The urine was normal. The concentration of hemoglobin was 85 per cent; the erythrocytes numbered 4,440,000 and the leukocytes 5,800 per cubic millimeter of blood. The flocculation test of the blood for syphilis was negative. Roentgenologic studies of the thorax and head gave evidence of nothing abnormal, but those of the stomach and duodenum revealed duodenal ulcer.

Neurologic examination gave evidence of marked disturbance of the patient's equilibrium. In walking he pitched backward or forward, held his legs wide apart for better support and could not walk without a cane. On trying the heel-to-knee test, however, he showed only slight incoordination, but general atony was present in all muscles of the limbs. When he was sitting there was some swaying, suggesting truncal ataxia; this was less marked than the ataxia of the lower extremities. When the patient used his hands there were obvious dysmetria and dyssynergia of motion; the finger-to-nose test was poorly performed, but there was not a marked degree of incoordination. Dysdiadokokinesis was present but was slight. The rebound phenomenon of Gordon Holmes was present, and the patient's handwriting was jerky and almost illegible. There was definite, coarse nystagmus both on upward and on lateral gaze. There were no paralysis of any limb and no spasticity, but on plantar stimulation there occasionally was dorsiflexion of the great toe on either foot. Tremor was absent, and hearing was normal. Tendon reflexes were everywhere diminished in amplitude, but all were present and the diminution seemed to be due to atony of the muscles. Sensory functions were everywhere preserved. Speech was somewhat jerky and staccato but quite intelligible.

Diagnosis.—The diagnosis was not clear at first because of the loss of weight, anorexia and weakness. A malignant condition was suspected, but no primary tumor was present. Accordingly, encephalitis involving the cerebellum or its tracts was suggested, and atrophy of the parenchyma of the cerebellar cortex was rejected as a possibility because of the short history, relatively rapid downward course and generally ill appearance of the patient. Finally, to clear up the diag-

nosis and to exclude all possibility of cerebellar tumor, surgical exploration of the cerebellum was advised.

Operation.—The posterior fossa of the skull was opened through a transverse incision on January 17. The dura was distended, but not under pressure, and a large amount of cerebrospinal fluid gushed forth when it was opened. The cisterna magna seemed about three times its normal size. There was obvious atrophy of both hemispheres of the cerebellum and of the vermis; the cerebellum was deep in the posterior fossa and was surrounded by cerebrospinal fluid. There was no increase in intracranial pressure, and the circulation of cerebrospinal fluid seemed normal. The vessels were large in contrast and seemed engorged.

Course.—The patient seemed to do well after operation until about the seventh day, when distention and tenderness of the abdomen developed. With this there were nausea and vomiting, and the patient gradually became weaker. His temperature increased to 102 F., and he became irrational, and in spite of all that was done he died on January 27, the eleventh day after operation.

Necropsy.—General peritonitis was present and had originated from the perforation of an acute pseudomembranous typhlitis. Amebas were not found in the base or walls of ulcers which were limited to the cecum. The scar of a healed duodenal ulcer was noted. Nothing of any significance was present in any of the other organs of the abdomen or thorax, except slight edema of the lungs. There was no gross lesion in the cerebrum; the vessels in the circle of Willis and their larger branches did not reveal arteriosclerosis, and anomalies were not seen. There was neither meningitis nor atrophy of the cerebrum. The cerebellum, however, was markedly atrophied, and there was an excessive amount of cerebrospinal fluid around it; the blood vessels were very prominent over its convexity, but the atrophy was uniform, so that the hemispheres had receded from the vermis, which, although it too was atrophic, appeared very prominent. The cerebellum, along with the midbrain, pons and medulla oblongata, weighed 150 Gm. Coronal sections through the cerebrum, midbrain, pons and cerebellum did not give evidence of hemorrhages or infarctions, and except for its small size the cerebellum seemed normal. The atrophy appeared to involve all portions of the cerebellum uniformly. The dentate nucleus seemed slightly more yellow than usual.

The brain had been fixed by vascular injection of a dilute solution of formaldehyde, U. S. P. (1:10), but small portions were removed, deformaldehydized and placed in formaldehyde-bromine solution for Cajal's and Hortega's impregnation methods. Small pieces from various parts of the hemispheres, vermis, dentate nucleus, pons, midbrain and medulla oblongata were placed in Weigert's mordants for Weigert's myelin sheath and Mallory's stains, and portions from these areas were also prepared for general stains (hematoxylin and eosin and Van Gieson's) as well as for toluidine blue staining and for the modified Bielschowsky silver impregnation method.

Microscopic examination of various portions of the cerebral hemispheres gave no evidence of encephalitis, and except for a few lymphocytes in the subarachnoid space of the left posterior parietal lobe there was no evidence of inflammatory reactions. The ganglion cells were normal, and there was no increase in the number or size of the glia cells. The ganglion cells of the basal nuclei were normal except for an excess of pigment in about a third of the large ganglion cells of the middle nucleus of the thalamus, but these cells were not degenerating.

Sections through the midbrain stained by the Weigert myelin sheath method indicated that all fiber bundles were intact and that myelin sheaths were normal. The astrocytes and oligodendroglia cells were normal; there was slight increase

in the number of normal microglia cells, although there were no compound granular corpuscles. The red nucleus on the right was normal except that there were two small foci of microglia intermingled with several astrocytes and oligodendroglia cells, such as are sometimes seen when there is acute degeneration of a ganglion cell. The red nucleus on the left and the substantia nigra on both sides were normal. There were some small collections of lymphocytes in the subarachnoid space of the interpeduncular fossa, and some of these collections were closely adherent and enmeshed in the adventitia of the larger veins. In addition to lymphocytes, there were some eosinophilic leukocytes and also some scavenger cells; the latter were not numerous. The pons was normal except that a small number of the nerve cells contained an excess of pigment. There was no inflammation in the medulla oblongata, and when this was stained with Weigert's myelin sheath stain it was seen that all fiber tracks were intact; with the modified Bielschowsky impregnation method the nerve fibers appeared normal. The toluidine blue stain disclosed that the nerve cells of the olive contained more pigment than is normally present in persons of this age, but the olivary nerve cells otherwise were normal and there was no degeneration. There were many microglia cells (rod cells) in the olive, but these were not active and there was no degeneration; scavenger cells were absent. The medulla oblongata and the spinal cord when stained with various stains evidenced no changes. Sections from various parts of the cerebellar hemispheres, the vermis and the dentate nucleus were examined, but the most advanced changes were present in the hemispheres.

In the left hemisphere sections from numerous areas showed similar changes. There were collections of lymphocytes in the subarachnoid space; the collections were larger and more numerous in the depths of the sulci, but no polymorphonuclear or eosinophilic leukocytes were present and scavenger cells were sparse. The arachnoid and its trabeculations were only slightly thickened, and there was no blood pigment. The molecular layer was thinner than normal, and there were several lymphocytes in the perivascular space of some small arterioles. With the Cajal gold chloride and sublimate method an excess of astrocytes was seen in this layer, sometimes in small groups. The Hortega silver carbonate method showed an excess of microglia cells scattered throughout the molecular layer; these were occasionally collected into small foci and tended to be arranged in irregular rows. A thionine stain showed even better the collections of glia cells in small groups; these collections were few and were not related to any of the blood vessels. They seemed to be arranged where the dendrites of the Purkinje cells had been, but such dendrites were not present.

The collecting of glia cells in this manner is a phenomenon which has been recognized and referred to as a *Gliastrauchwerk*, and it is characteristic of recent and acute degeneration of ganglion cells and their dendrites (figs. 1 and 2). With the modified Bielschowsky stain it was seen that there were no dendrites of the Purkinje cells and that there was complete absence of these Purkinje cells from the entire left hemisphere; there were no remnants of these cells, and thionine and other stains confirmed this observation. The modified Bielschowsky method also gave evidence of almost complete absence of tangential nerve fibers, although there were numerous fibers projecting at right angles from the granular layer into the molecular layer. The basket cells which normally surround the Purkinje cells were in an excellent state of preservation and were, in fact, normal though empty (fig. 3). There was an excess of normal glia cells in the Bergmann layer. The Cajal gold chloride and sublimate method showed that practically all the cells in this layer were astrocytes, which were so numerous as to form a mesh in which it was impossible in most places to distinguish the individual cells and their proc-

esses (fig. 4). There were no microglia or scavenger cells present. In the case previously reported by us we noted some immature nerve cells in the deeper part of the molecular layer and in the granular layer, but in this case no such cells were present. The granular layer was atrophied to approximately one-half its normal size, and the cells were widely separated. In this layer there were many large astrocytes, but no scavenger cells. The white matter beneath the granular layer was normal, except that the oligodendroglia cells were swollen, giving the tissue a honeycomb appearance; the myelin sheaths and the axis-cylinders were intact. There were more large astrocytes scattered diffusely throughout the white matter. These cells were most numerous where the myelin-

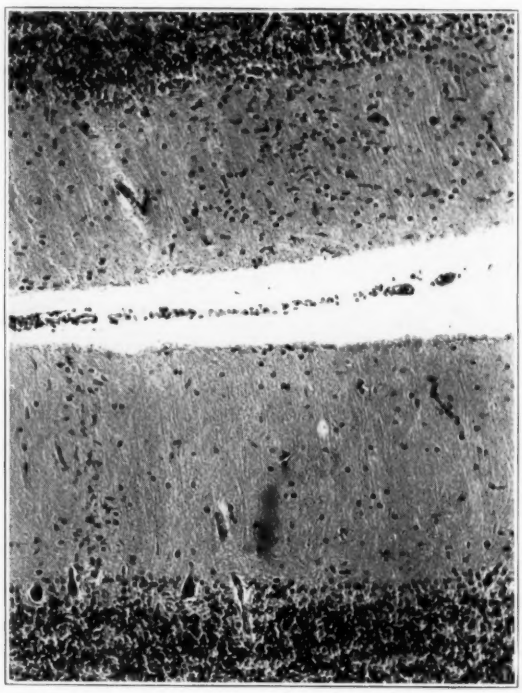

Fig. 1.—The slight meningeal reaction may be noted. Only three Purkinje cells remain, and one is undergoing degeneration with a well marked glial reaction. There is a diffuse glial reaction in the molecular layer of the other convolution. Hematoxylin and eosin; × 90.

ated tissue emerged from the granular layer. With Mallory's phosphotungstic acid-hematoxylin stain it was noted that there was no increase in connective tissue in any part of the left hemisphere and that the walls of blood vessels were normal. Blood pigment was absent from the perivascular spaces.

In the right hemisphere there were collections of cells in the subarachnoid space: most of these were lymphocytes, but there were also plasma cells and some scavenger cells. The pia-arachnoid and the connecting trabeculae were not thickened, and the blood vessels were normal. In many places the molecular layer of the lateral surface of the hemisphere was markedly atrophied, much more so than

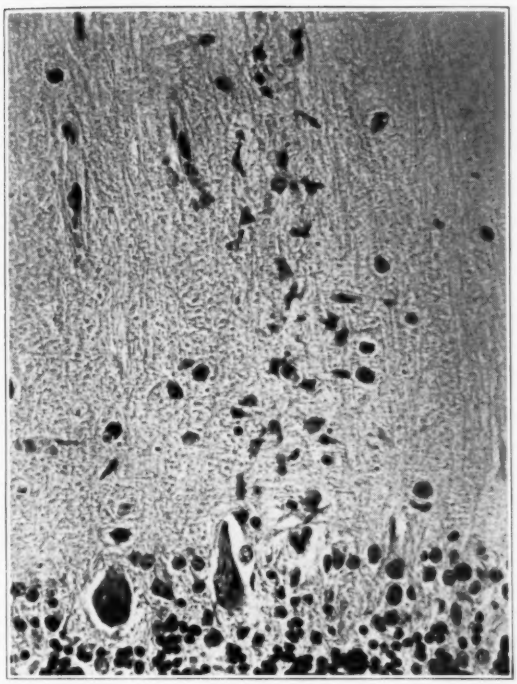

Fig. 2.—A well marked and characteristic glial reaction (*Gliastrauchwerk*) may be seen, the result of destruction and degeneration of one of the Purkinje cells. There are two mitotic figures in the glial structure. Hematoxylin and eosin; × 275.

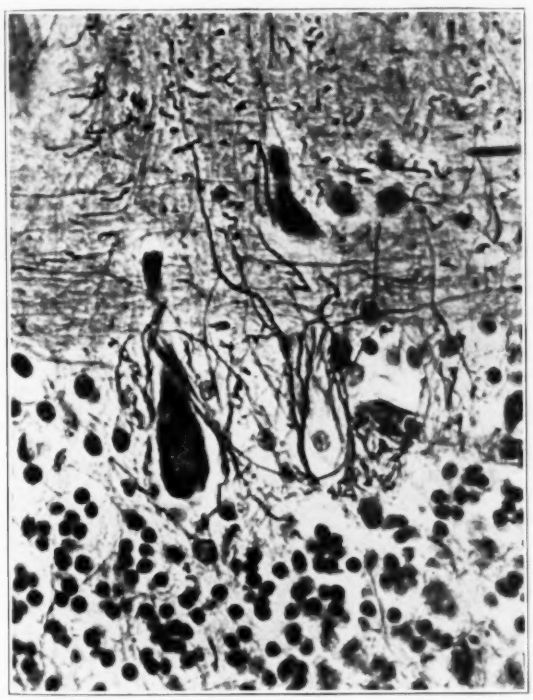

Fig. 3.—Basket cells may easily be seen around the degenerating cell as well as around the place where a cell had once been. The nucleus in the empty basket cell belongs to an astrocyte. Modified Bielschowsky method; × 500.

that of the left hemisphere. In this layer there were many microglia cells (fig. 5), astrocytes, endothelial cells and, occasionally, small collections of lymphocytes. There were also groups of astrocytes, microglia, lymphocytes and endothelial-like cells collected along the course where the dendrites of the Purkinje cells had been. Examples of this *Gliastrauchwerk* were common and were more pronounced than in the left hemisphere, so that the degeneration of ganglion cells and their dendrites seemed to be of more recent occurrence. The thionine stain demonstrated this clearly. Tangential fibers had for the most part disappeared, and there were no dendrites of the Purkinje cells. There were a few fibers projecting toward the meninges, but these were delicate and unbranched and were not dendrites of Pur-

Fig. 4.—There is a marked increase of astrocytes, particularly in Bergmann's layer and, to a lesser extent, in the deeper portion of the molecular layer. Cajal's gold chloride and sublimate method; × 200.

kinje cells. There were no Purkinje cells in this hemisphere, but with the modified Bielschowsky method the basket cells were seen to be in an excellent state of preservation (fig. 3). As in the left hemisphere, there was an excess of glia cells in the Bergmann layer, presumably replacing the destroyed Purkinje cells. The granular layer was atrophic and much smaller than normal, and in the portion remaining fewer cells than normal were present. Many delicate axis-cylinders were seen coursing through this layer from the basket cells toward the white matter. These axis-cylinders were normal and well preserved. The white matter contained normal myelin sheaths, and the axis-cylinders were normal. There were numerous large astrocytes, and microglia were abundant, but there were no scavenger cells. Many of the perivascular spaces contained collections of lymphocytes

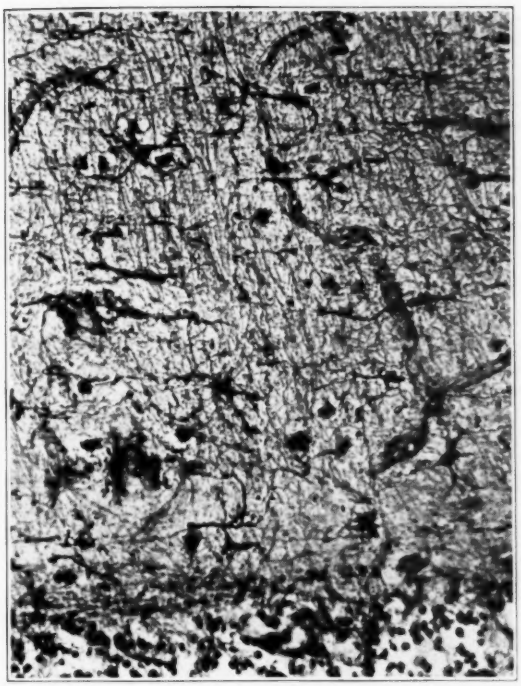

Fig. 5.—Increase of microglia cells in the molecular layer. The Purkinje cells had completely disappeared from this portion of the cerebellum. Hortega's silver carbonate method; × 250.

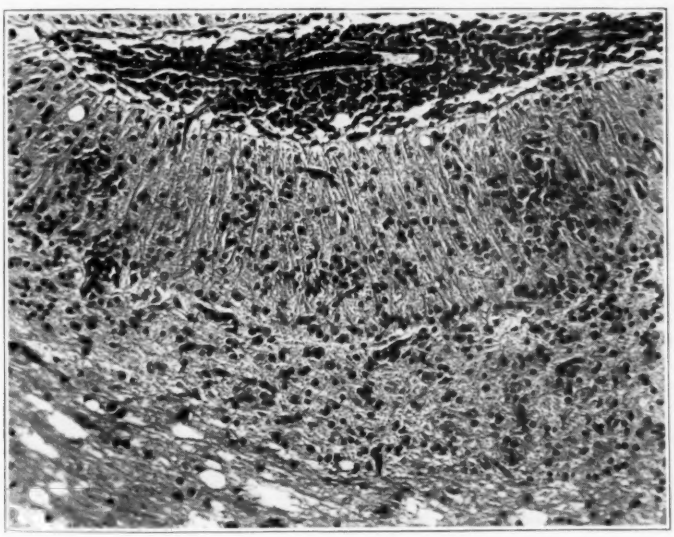

Fig. 6.—Section from the cerebellum of a nonimmunized monkey five days after inoculation with the virus of louping ill. Meningitis and destruction of the Purkinje cells and cells of the granular layer may be noted. There is glial and mesodermal proliferation in the molecular layer. Hematoxylin and eosin; × 135. Courtesy of Dr. T. Rivers, Rockefeller Institute for Medical Research.

and plasma cells. Some of the spaces contained large endothelial cells. The walls of the blood vessels were not thickened, and there was no increase of connective tissue anywhere.

In the vermis the lesions were less advanced than in the hemispheres, and there were collections of lymphocytes in the subarachnoid space. The molecular layer was atrophied but to a lesser degree than in the hemispheres; around some vessels there were collections of lymphocytes and some endothelial cells but no scavenger cells. There were numerous microglia cells scattered diffusely through the entire molecular layer, and there was also an increase of astrocytes, but these were not as prominent as the microglia cells. Tangential fibers were reduced in numbers. In a small number of folia there were some Purkinje cells, but few of them were normal, as the dendrites were reduced in size and numbers and many of the cell bodies were indistinct in outline. Around these cells the baskets were well preserved, as they were also in areas from which the Purkinje cells had disappeared.

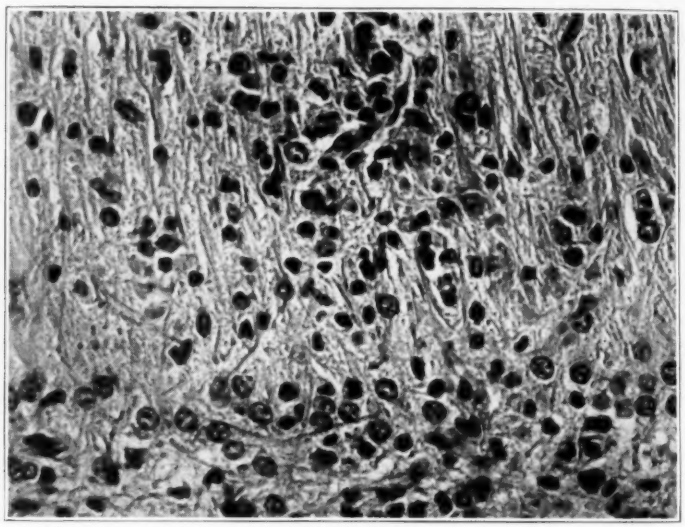

Fig. 7.—A higher magnification (× 400) of the section shown in figure 6. The glial and mesodermal reactions in the molecular layer and occasional mitotic figures may be seen clearly.

There was no increase of glia cells around the dendrites of the remaining Purkinje cells, and in these areas there were no lymphocytes around the blood vessels; the increase of microglia cells was also absent. However, there was an increase of astrocytes in the Bergmann layer, even where the Purkinje cells were present. These cells were much reduced in numbers and between them was an excess number of astrocytes, so that this layer was much more prominent than normal. The granular layer was slightly reduced in thickness, and there was a slight increase in astrocytes, but axis-cylinders coursed between the cells in a normal manner. The myelin sheaths of the underlying white matter were normal, as were the axis-cylinders. In the white matter there were perivascular collections of lymphocytes, plasma cells and endothelial cells, some of which contained granules of blood pigment. The walls of the vessels were normal. Aside from the mesodermal cells in the perivascular spaces, there were numerous similar cells scattered diffusely

throughout the white matter and in places collected into foci with no apparent relationship to blood vessels.

The ganglion cells of the dentate nucleus were normal in numbers and in distribution, but there was more pigment in the cytoplasm than is ordinarily found among persons of this age. Some cells were distended with pigment granules to a marked degree; otherwise they were normal. However, there was a marked glial reaction throughout the nucleus, and most of these cells were microglia. These were in various stages of activity, although there were no fully formed scavenger cells. There were also more astrocytes than normal and many of these were undergoing clasmatodendrosis, but they had not yet formed *gemästete* glia. These

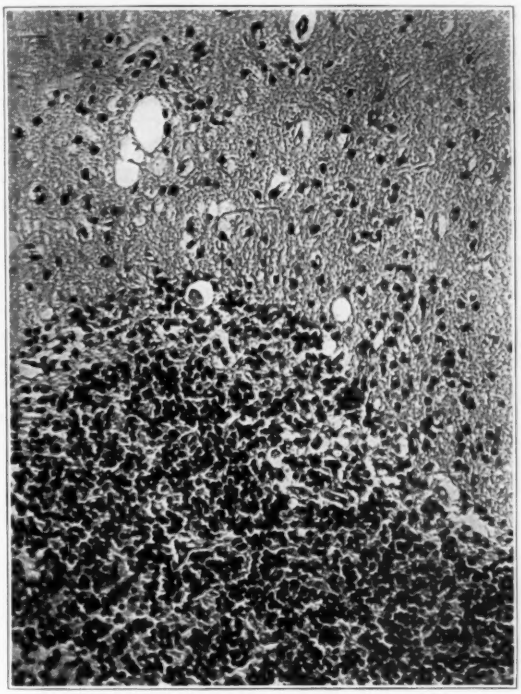

Fig. 8.—Section from the cerebellum of a monkey partially immunized against the virus of louping ill and later inoculated with the virus of this disease. The animal was killed thirty days after inoculation. There are extensive destruction of the Purkinje cells and a glial reaction in the molecular layer. Hematoxylin and eosin; × 150. Courtesy of Dr. T. Rivers, Rockefeller Institute for Medical Research.

cells were in the hilus of the nucleus and surrounding it. In addition to glial proliferation there were numerous lymphocytes, some plasma cells and many endothelial cells intermingled with the glia cells; this reaction was especially marked in the perivascular spaces, but was also noted in numerous small foci apparently unrelated to blood vessels. In some of the arterioles and venules there was proliferation of the lining endothelium, and around some there appeared to be proliferation of the cells in the adventitial spaces; these cells were morphologically indistinguishable from fibroblasts.

Through the courtesy of Dr. Thomas Rivers of the Rockefeller Institute we had the privilege of examining sections of the cerebellum of two monkeys inoculated with the virus of louping ill. The first monkey had died a few days after the virus had been inoculated, and there was diffuse encephalitis of the cerebellum with associated meningitis (fig. 6). The encephalitis had involved the entire cerebellum. All the Purkinje cells had disappeared, and in places there was destruction of many of the cells of the granular layer (fig. 7). In addition, there were some excellent examples of *Gliastrauchwerk* along the course of the dendrites of some of the Purkinje cells. The second monkey had been inoculated after partial immunization and had been killed at the end of thirty days. In the cerebellum practically all traces of encephalitis had disappeared, and the structure of the cerebellum was well preserved, although most of the Purkinje cells had disappeared (fig. 8). Some of these remaining cells did not seem to be in a normal healthy state, as their dendrites were diminished and some had disappeared completely. There was some increase of the glia cells in Bergmann's layer, but there were few good examples of *Gliastrauchwerk* along the course of degenerating or degenerated dendrites.

COMMENT

The clinical picture in this case was that of some general noxious condition that caused the patient to lose strength and weight and that also had a specific influence on his cerebellar system, in that it was conspicuously injured. The whole illness from onset to death lasted almost twelve months. It was insidious in onset and steady in progress and seemed in general to present a fairly clearcut clinical syndrome. Nevertheless, the novelty of such a phenomenon caused some doubt as to the diagnosis. There was no evidence of increased intracranial pressure, yet the periods of spontaneous projectile vomiting suggested compression of the medullary centers. The history and roentgenologic findings of duodenal ulcer seemed unassociated with the patient's principal complaint. Exploration of the cerebellum was advised mainly to clear up the diagnosis of a disease that seemed definitely to be running a fatal course. Some precedent for this might be seen in the case of Alajouanine and his co-workers [10] in which a youth aged 20 presented a progressive cerebellar syndrome but, unlike our patient, toward the end had papilledema, headaches and manifest evidence of increased intracranial pressure. At operation marked cerebellar atrophy was found, and a piece of cerebellar tissue was removed for diagnosis. Another dis-

10. Alajouanine, T.; Bertrand, I., and Thurel, R.: Sur un cas d'atrophie cérébelleuse avec un trouble spécial de la tonicité musculaire (muscle caoutchouc) biopsie du cervelet au cours d'une intervention pratiquée à l'occasion d'un oedème papillaire survenu au cours de l'évolution, Rev. neurol. **1**:504 (April) 1933.

similar feature in Alajouanine's case was the finding of diffuse inflammatory changes in the piece of tissue removed; these changes had involved indiscriminately all layers of the cerebellar cortex. Our case, however, resembles fairly closely not only the other case previously reported by us, but also Murri's case which was described some years ago. In all these cases there was a relatively short history of between nine and eighteen months' general ill health and a fatal termination. Gastroenteritis might be considered as a cause of debility in Murri's case, and our other patient had pelvic carcinoma. In this more recent case, however, nothing else was found which could have caused the patient's rapid decline other than the specific condition that made him lose weight and strength and destroyed the Purkinje cells of his cerebellum. The duodenal ulcer was merely an associated phenomenon, and the perityphlitis with general peritonitis, a terminal event. The other ten cases reported in the literature seem rather different, in spite of the fact that all were characterized by progressive atrophy of the cerebellum and, more particularly, of the Purkinje cells. In them the course of the disease was quite long—of many years' duration; the patients did not suffer general ill health but died from some intercurrent disease.

Our case also is different from the previously reported cases reviewed by us in that microscopically there were processes still active which with good reason could be called encephalitis. The lesion in the hemispheres was more advanced, and thus possibly older, than that in the vermis, where signs of encephalitis were most marked. It is true theoretically that the perivascular collections of cells might be the result of tissue degeneration and not be of a truly inflammatory nature, but the other findings suggest an inflammatory cause for the degeneration of the cells. Encephalitis confining itself to the cerebellum and not affecting other portions of the brain is rare, and such specificity brings up many problems. Chief among these is the search for analogies, if not in human, at least in animal, subjects. Louping ill, a disease endemic in sheep in the border counties between England and Scotland, is caused by a virus which has been isolated, and the disease has been reproduced in monkeys, mice and swine.[11] In cases of sheep naturally affected, the disease, while it is more or less diffuse over the whole central nervous system, affects the Purkinje cells of the cerebellum severely and conspicuously. In higher animals, such as monkeys, which were success-

11. Brownlee, A., and Wilson, R. D.: Studies in the Histopathology of Louping Ill, J. Comp. Path. & Therap. **45**:67, 1932. Pool, W. A.; Brownlee, A., and Wilson, R. D.: Etiology of "Louping Ill," J. Comp. Path. & Therap. **43**:253, 1930. Rivers, T. M., and Ward, S. M.: Cultivation of Louping Ill Virus, Proc. Soc. Exper. Biol. & Med. **30**:1300 (June) 1933. Schwentker, F. F.; Rivers, T. M., and Finkelstein, M. H.: Observations on the Immunological Relation of Poliomyelitis to Louping Ill, J. Exper. Med. **57**:955 (June) 1933.

fully inoculated by Hurst,[12] Findlay [13] and Rivers,[14] there is an even more conspicuous involvement of the cerebellum and Purkinje cells. Further, the animals were obviously ataxic and showed muscular incoordination prior to death. The sections of the cerebellum of one monkey inoculated with the virus of louping ill, which we were privileged to examine, revealed acute diffuse encephalitis involving all parts of the cerebellum, particularly attacking and destroying all the Purkinje cells. The second monkey, partly immunized against louping ill, was recovering from an inoculation of this virus and presented a subacute stage of the disease; the changes in the cerebellum resembled those seen in the patient we have just described. Rivers and Schwentker [15] have described louping ill in man. Four of their assistants while working with the virus of louping ill contracted encephalitis from which they recovered. Nevertheless, the virus of louping ill could not be recovered from the spinal fluids, and the patients did not have any symptoms of extensive or specific involvement of the cerebellum.

The reactions in the cerebellum in the present case correspond to those associated with virus disease in general and here were limited to the cerebellum alone, particularly to the Purkinje cells; even the fiber tracts to and from the cerebellum were intact. The glial reaction of the Bergmann layer can be considered in the nature of a replacement gliosis and not necessarily as the result of a reaction to a virus, although that is possible. The so-called *Gliastrauchwerk* is considered the result of an inflammation which has brought about degeneration of ganglion cells and their dendrites. Senile degeneration of cells does not produce any inflammatory reaction, and alcohol or any of the heavy metals do not specifically attack the Purkinje cells of the cerebellum. In suggesting a virus as the etiologic agent in some of these cases of atrophy of the cerebellum we recognize that we depended on histologic signs alone, since we did not have the opportunity to recover the virus or to attempt the reproduction of similar lesions in animals. Nevertheless, considering the clinical course and the pathologic changes, at least in this more recent case, we think that there is sufficient evidence to suggest strongly that the condition is a virus disease. The two other cases, one described by us and the other by Murri, could also fit into this category by reason of the subacute nature of the process. The remaining eleven cases, by

12. Hurst, E. W.: The Transmission of Louping Ill to the Mouse and the Monkey: Histology of the Experimental Disease, J. Comp. Path. & Therap. **44**: 231, 1931.

13. Findlay, G. M.: The Transmission of Louping Ill to Monkeys, Brit. J. Exper. Path. **13**:230 (June) 1932.

14. Rivers, T. M.: Personal communication to the authors.

15. Rivers, T. M., and Schwentker, F. F.: Louping Ill in Man, Proc. Soc. Exper. Biol. & Med. **30**:1302 (June) 1933.

reason of the chronicity of the disease, do not justify such hypothesis unless one accepts a chronic type of virus disease and rejects all other possibilities. We hope that this contribution will serve to draw attention to the disease and that in the future when it is recognized clinically experimental work with the spinal fluid or tissue may settle conclusively the etiologic agent at fault.

DISCUSSION

DR. ARTHUR WEIL, Chicago: I think it was Hans-Joachim Scherer who a few years ago published his studies on glial reaction in localized cerebellar disease. He pointed out that the ideas of earlier investigators were not substantiated by his own studies that the *Gliastrauchwerk* indicates the reaction to a specific etiologic agent. We have recognized such aspecific stereotyped pattern of reaction to a variety of damaging factors, e. g., for the Betz cells which react with central chromatolysis to numerous different etiologic factors. In a similar way the formation of a *Gliastrauchwerk* may follow disease and degeneration of the Purkinje cells and their dendrites under manifold conditions.

I think, therefore, that one should be rather hesitant in drawing the conclusion that in the case which was presented the peculiar glial reaction indicated a subacute cerebellar encephalitis produced by a virus and to suggest its analogy to virus disease in animals.

DR. GEORGE B. HASSIN, Chicago: In many cases of the type of cerebellar atrophy demonstrated by Drs. Parker and Kernohan, not only the Purkinje cells but other ganglion cells—stellate, Golgi II, basket and granular layer cells—of the various cerebellar layers are atrophied. The atrophy results in a formation of a glial scar and in no way differs from the cerebral atrophy seen in Pick's disease. In my patients, aged 27 and 32, respectively, who exhibited a far greater destruction of the cerebellum than that in the cases of Dr. Parker, cerebellar symptoms were entirely lacking. Nor are the etiologic factors uniform. Sherer, for instance, mentioned thirty etiologic factors so that louping ill will have to be considered the thirty-first.

DR. HARRY L. PARKER: In the earlier cases reported of this disease, there was a little different picture and that picture was a more slowly progressive destruction of the Purkinje cells with little or no evidence of inflammation and with practically an intact cerebellum otherwise. Different etiologic factors were discussed by the various observers. Alcohol was considered, infection and infection on an atrophic cerebellum, and, last of all, a simple senile degeneration. I quite agree that it is possible that there are a large number of possible etiologic factors in this type of disease, the so-called cortical parenchymatous cerebellar atrophy. However, this last case presented was a little different from the older cases inasmuch as the progress was more rapid and there was a little more evidence of a subacute inflammatory process in the cerebellum.

The subject is a fascinating one, I think, inasmuch as relatively speaking there are not very many acute processes of an inflammatory nature that hit the cerebellum specifically. I am sure, as Dr. Kernohan says, we will have more cases in the future so that we can study a little more extensively disease of the cerebellum of inflammatory or toxic-infectious type.

SIGNIFICANCE OF PANIC AND STATES OF CONSCIOUSNESS IN GRASPING MOVEMENTS

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As an aid in localizing cerebral lesions, symptoms and objective manifestations play an important rôle. These must, therefore, be meticulously evaluated, for when obscure they cause confusion and lead to errors in localization. From time to time new signs are described, and varying degrees of importance are attached to them. In recent years the frontal lobe has been assigned a new function.

The so-called reflex grasping or forced grasping and the synonymous terms used to designate these motor phenomena, such as "tonic innervation," *Zwangsgreifen,* "groping" and "pointing," have created considerable discussion.

It is not the purpose of this communication to give an exhaustive review of the literature. An analysis of some of the recorded data is, however, essential.

Wilson and Walshe,[1] in describing the phenomenon, called it "tonic innervation." Patients with hemiparesis showed, on voluntary flexion and extension of the involved arm, a considerable delay in relaxation associated with an inability of the hand to release the grasp of an object held in it. When the observer attempted to extract the object forcibly an increase in the strength of the grasp followed immediately. This persisted until the forcible attempt ceased. If there was no attempt to extract the object by force, the hand opened with no difficulty.

Riddoch and Brain [2] described a similar phenomenon but regarded it as a palmar reflex, with the touch on the palm acting as the stimulus.

About the same time Schuster and Schuster and Pineas,[3] after extensive studies, noted these phenomena and added certain observations. The hand, they stated, grasped involuntarily, even against the patient's will, at any object that touched the palmar aspect of the hand or digits. Further, the hand and arm turned actively toward the stimulating object and followed it as though it were a magnet. Even before contact with

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From the Neurological Service, Mount Sinai Hospital, New York.

Read by title at the Sixtieth Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 4, 1934.

1. Wilson, S. A. K., and Walshe, F. M. R.: Brain **37**:199, 1914.

2. Riddoch, G., and Brain, W. R.: Brain **46**:246, 1923.

3. Schuster, P.: Ztschr. f. d. ges. Neurol. u. Psychiat. **83**:586, 1923. Schuster, P., and Pineas, H.: ibid. **91**:16, 1926. Schuster, P.: ibid. **108**:715, 1927.

the palm was made, the hand involuntarily grasped at the object, and when the object was withdrawn from its grasp the hand grasped it or followed it.

Adie and Critchley [4] noted in addition that the hand and arm and even the trunk were actively turned toward the stimulating object when the palm was touched, and when this was done repeatedly the limb was drawn in any direction as though by a magnet, even when the patient's eyes were closed. They stated also that the patients in whom these movements were seen were psychically normal at the time of their occurrence and that the phenomena occurred without the conscious knowledge of the patient, though, paradoxically enough, he was said to be annoyed by them.

The subject has also been discussed in comprehensive communications by Freeman and Crosby,[6] Janischewsky,[7] and Kleist.[8]

Experimental study of the grasping phenomenon has also received considerable attention from physiologists.

Richter and Hines [9] found that ablation of the intermediate precentral region of the cortex (premotor area, Brodmann's area 6) is followed by the development of a grasp reflex. This consists of tonic grasping when the animal is hung by one hand from a horizontal bar and may be elicited for as long as twenty-one days after operation. The reaction is crossed, but bilateral ablation of the relevant cortical region gives a stronger response in each hand than can be obtained in either hand by unilateral ablation.

Robinson [10] found that a new-born infant is able to support its own weight when grasping a horizontal rod. He examined a series of infants and found that the majority could hang in this manner ten seconds or more and that one infant was able to support itself for two minutes and thirty-five seconds. He attributed this to a primitive response seen in monkeys and apes in which the new-born animal holds on to the hair on the under-surface of the mother's body. Richter [11] studied this response in new-born monkeys and found that they showed a grasping response that was uniformly stronger than that of new-born human infants. While the longest period that a human infant could hang supported by both hands was two minutes and thirty-five seconds, one

4. Adie, W. J., and Critchley, M.: Brain **50**:142, 1927.
5. Footnote deleted by author.
6. Freeman, W., and Crosby, P. T.: Reflex Grasping and Groping, J. A. M. A. **93**:7 (July 6) 1929.
7. Janischewsky, A.: Deutsche Ztschr. f. Nervenh. **102**:177, 1928.
8. Kleist, K.: Monatschr. f. Psychiat. u. Neurol. **65**:317, 1927.
9. Richter, C. P., and Hines, M.: Am. J. Physiol. **101**:87, 1932.
10. Robinson, L.: Nineteenth Century **30**:831, 1891.
11. Richter, C. P.: The Grasping Reflex in the New-Born Monkey, Arch. Neurol. & Psychiat. **26**:784 (Oct.) 1931.

monkey was able to support itself by one hand for thirty-five minutes. Richter and Paterson [12] found that under the influence of certain drugs a grasping response could be induced in adult monkeys. This was accomplished first by hypodermic injections of bulbocapnine (1931) and later by the inhalation of carbon dioxide (1932) in high concentrations. Recently (1933) a large series of drugs was used in these experiments. The grasp reflex could be elicited with sixteen of the twenty-three drugs used. All these drugs had a depressant action on the cerebrum, causing either a stuporous state or a marked reduction in responsiveness. The drugs which are primarily stimulants required large doses, sufficient to produce a depressant action. If, however, they were given in small doses, cerebral stimulation resulted, and the grasping phenomena could not be elicited. In this connection the records obtained after injection of amytal are interesting. Grasping movements were entirely absent during the period of sleep, which lasted four hours, but were present for a short time, first, before the animal fell asleep and again for a while during waking.

Richter and Paterson stated that it is not possible at present to determine definitely how these drugs bring about the grasp reflex in adult animals. They assumed, however, that depressants paralyze the mechanisms of the frontal lobe and block the pathways from the frontal lobe to the motor centers in the cortex or those from the lobe to the lower centers. They added: "That the frontal lobes are involved would seem to be indicated by the fact that the animals are usually stuporous when the reflex is present."

Grünbaum,[13] in discussing the pointing position of the hand, directed attention to its association with grasping and groping. He noted that stretching the index finger produces flexion of the other fingers and often influences the opposite extremity, producing a similar pointing position. This pointing position of the hand appears when active grasping, which he suggested is biologically the more primitive, is either suppressed or prevented by external conditions. He therefore assumed that the pointing position is modified grasping and that it probably originated phylogenetically as an enfeebled and modified act of grasping in trying to secure an object which is beyond reach by extension of the fingers and arm. He added that there are greater tonus and flexion in grasping than in pointing. He called attention to the fact that when angry or argumentative one often points with the index finger extended and the thumb and the last three fingers flexed. If, however, the discussion becomes tinged with greater emotion, the index also flexes, and the hand assumes a position as though grasping the opponent. He con-

12. Richter, C. P., and Paterson, A. S.: J. Pharmacol. & Exper. Therap. **4**:677, 1931; Brain **55**:391, 1932.

13. Grünbaum, A. A.: Brain **53**:267, 1930.

cluded that "everything points towards the conclusion that particular mechanisms such as grasping and pointing form a unity and should be considered as physiological mechanisms and as modes of behavior."

To the frontal lobe has been ascribed the more important rôle in the production of forced grasping. The phenomenon is regarded as a release, and Schuster and Casper [14] stated that it can occur only with an intact pyramidal tract. They were further of the opinion that in order to produce forced grasping impulses from both frontal lobes must be blocked. In all their cases there was involvement of the anterior part of the corpus callosum.

Fulton,[15] in his experiments, obtained grasping as a permanent sign only in animals in which the pyramidal tract had been completely destroyed. He offered an explanation for this apparent paradox:

> In chimpanzees, which neurologically are nearer human beings than monkeys are, forced grasping is generally well developed for from ten days to two weeks after a lesion is restricted to the premotor area. It is associated incidentally with spasticity of the extremities and with marked increase of the tendon reflexes. If the adjacent motor area is removed from such an animal during the period in which forced grasping is present, the opposite extremities lapse into a state of profound flaccid paralysis with absence of tendon reflexes and disappearance of forced grasping. In the course of five or six days, however, the tendon reflexes return, the extremities again become spastic, and soon afterwards forced grasping once more appears; well developed grasping is never present, however, until appropriate lesions have been made in the opposite hemisphere. In man, one is not likely to see forced grasping in association with a pyramidal lesion, since the depression of reflexes resulting from destruction of the pyramidal tract is undoubtedly greater in the acute phase, e.g., after a capsular hemiplegia, than it is in the chimpanzee, and the stage of reflex recovery from the pyramidal lesion probably comes after a greater interval than that required for pure premotor grasping to disappear spontaneously.

Most authors, then, in discussing the significance of this phenomenon have begun to look on it as an indication of involvement of the frontal lobe. Adie and Critchley [4] definitely stated that when present in a patient with cerebral tumor it is unequivocal evidence of disease of the frontal lobe.

Bucy [16] has, however, reported two cases in which the primary tumor was remote from the frontal lobe. Though it is unquestioned that in both his cases the brain was subjected to severe pressure, it seems equally certain that a psychic disturbance also was a significant feature, a condition that will be demonstrated as present in practically all the other reported instances in which grasping phenomena have been observed.

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14. Schuster, P., and Casper, J.: Ztschr. f. d. ges. Neurol. u. Psychiat. **129**: 739, 1930.

15. Fulton, J. F.: Forced Grasping and Groping in Relation to the Syndrome of the Premotor Area, Arch. Neurol. & Psychiat. **31**:221 (Feb.) 1934.

16. Bucy, P. C.: Brain **54**:480, 1931.

The first patient described by Bucy was a man, aged 48, who on admission was too stuporous and uncooperative to give a satisfactory history or to permit determination of the visual fields. There was definite and obvious grasping in both hands. Whenever an object was drawn across the palm of the patient's hand, the fingers closed on it and grasped it firmly. Efforts to withdraw the object caused the force of the grasp to increase. At operation a tumor of the right occipital lobe was exposed and partially removed. The patient became considerably brighter, and almost two months after operation the visual fields were determined and showed complete left homonymous hemianopia. Though complete left hemiplegia developed, reflex grasping was never elicited after the operation.

The second patient was a young girl who presented signs and symptoms of markedly increased intracranial tension. Clinically, there were few focal signs except paralysis of the upward movements of the eyes and marked bilateral reflex grasping. Whenever her hand caught on clothing or when an object, such as the handle of a reflex hammer or the examiner's fingers, was drawn across her palm, the fingers immediately closed firmly on the object, and any effort to withdraw the object caused the grasp to tighten. She died before an operation could be performed, and necropsy revealed severe internal hydrocephalus, due to obstruction of the ventricular system by an ependymoma in the posterior portion of the fourth ventricle. It is evident from this partial description that she was not in full possession of her mental faculties.

It is of interest that the first patient, who had undergone only partial extirpation of a tumor of the occipital lobe, showed reflex grasping only before, and never after, the operation, even though the tumor was not removed and continued to grow to such an extent that it involved the region of the internal capsule and the thalamus and occupied the anterior inferior part of the right occipital lobe, the posterior portion of the temporal lobe and a small part of the posterior inferior area of the parietal lobe. It is also of importance that prior to operation the patient was too stuporous and uncooperative to give a satisfactory history and that determination of the visual fields was impossible. At the time, prior to operation, when such a mental state existed, forced grasping was present. The report stated, however, that after the operation the patient was considerably brighter, so much so that almost two months after the operation he was sufficiently cooperative to allow the determination of the visual fields. In this period there was never forced grasping.

It is interesting to note at this point that Walshe and Robertson,[17] in commenting on the observations of Adie and Critchley [4] that there were groping and grasping after the examiner's hand even when the patient's eyes were closed, remarked that a tactile stimulus is effective only at the moment of contact. Before the touch of the examiner's finger is actually felt and after the finger has left the patient's palm, no stimulus is acting; no one can anticipate the direction from which the stimulating finger is approaching or determine the direction in

17. Walshe, F. M. R., and Robertson, E. G.: Brain **56**:40, 1933.

which it is retreating unless it is seen throughout the whole procedure; that the hand of the patient without vision should advance to and follow the stimulating finger is impossible. Equally inexplicable is the statement that these complex movements, even when directed by vision, may be made by a psychically normal person without his being aware of the fact. They remarked further that, though Adie and Critchley stated that all their patients were psychically normal, reference to the cases reported in their paper shows that two of the patients were grossly abnormal. They added that all Schuster's patients were mentally reduced. With lesions localized in the frontal lobe, it is to be expected that disorder of psychic control would be present.

Walshe and Robertson stated:

> Of all our cases, we may make this generalization, namely, that all showed some unequivocal signs of impairment of psychical function, some signs of dissolution of function in the highest cerebral centers, and we believe this to be an invariable concomitant of grasping movements, and probably also of tonic innervation. They are, in fact, volitional movements occurring in individuals whose psychomotor functions have been reduced by disease of the brain to the production of the "least voluntary" and "most automatic" movements. They occur only in the conscious patient, and disappear with the development of stupor or coma.

PERSONAL OBSERVATIONS

On a number of occasions I have made observations that have led to an analysis of the underlying mechanism for these grasping phenomena.

For several months a young salesman had been disturbed by attacks occurring usually in the night. He was awakened by extreme precordial distress; he was conscious of palpitation, perspired profusely, felt alternately hot and cold, had a sense of impending disaster and panic and in each attack "almost" fainted, though this never occurred. On examination, with the exception of bounding pupils that contracted and dilated when light was directed on them, generalized hyperreflexia and extreme dermographia, there were no demonstrable objective findings. During the examination, however, he suddenly indicated that an attack was coming on; the face appeared flushed; beads of perspiration were noted on the forehead; he screamed "I'm fainting" and grasped the examiner's hand so tightly that the greater the effort to extract the fingers, the firmer the grasp became. He was reassured, and soon the grasp lessened. He was subsequently seen on several occasions and eventually improved, so that the troublesome symptoms rarely recurred. He was regarded as presenting a syndrome of imbalance of the autonomic nervous system. Certainly there was no pathologic change in the frontal lobe.

A child with tuberculous meningitis, seen at a time when she was still conscious though semistuporous, presented a typical bilateral grasp. When the examiner's finger was placed in her palm, the fingers closed on it, and attempts to withdraw it only made the grasp stronger.

A man in the acute stage of cerebral hemorrhage was in a deeply comatose state with Cheyne-Stokes respiration and right hemiplegia. He presented no symptoms of grasping during this stage. Twelve hours later he was semistuporous, moaned, was restless and moved the left extremities actively; the entire right

side was paralyzed and spastic. Tendon reflexes were more active on the right. Abdominal reflexes were not elicited on the right, but a Babinski sign and ankle clonus were obtained on that side. When the examiner's finger was placed in the right palm, the finger closed spasmodically on it and maintained the grasp, despite a vigorous attempt to remove the digit. About a week later, when the patient was convalescent and fully conscious, there was no grasping. Several years later he presented right hemiparesis, with signs suggesting lesion of the pyramidal tract, and was still partially aphasic, but there were no evidences of grasping movements.

Two cases recently observed in the neurologic service of Dr. Israel Strauss at the Mount Sinai Hospital are instructive.

L. Z., a woman aged 58, was admitted to the hospital on March 22, 1934. For two and a half years she had had generalized convulsive seizures, incontinence, loss of consciousness and frequent biting of the tongue. A gradual change in personality, with a tendency to euphoria and facetiousness, had been noted, and there was marked impairment of memory. A defect in speech had been noted, with a tendency to the use of wrong words. There had been increasing drowsiness, and when admitted to the hospital the patient was in a comatose condition. Examination revealed mild papilledema in the left eye and slight changes in the right disk with scattered hemorrhages. There were weakness of the right external rectus muscle and a questionable flatness on the right side of the face; the tendon reflexes were hyperactive; the abdominal reflexes could not be elicited, and there was a definite Babinski sign on the left. A spinal tap revealed clear fluid under a pressure of 260 mm. Serologic tests of the blood and spinal fluid gave negative results. The diagnosis of a tumor of the frontal lobe was made, but because of the bilateral signs injection of air was performed. However, no air was visualized by roentgenograms of the skull. Bronchopneumonia developed and after several days the patient died. Necropsy revealed a large meningioma of the entire left frontal lobe.

With such a large tumor of the frontal lobe, one would expect grasping movements. These were not seen at any time. It is noteworthy that the patient was in a comatose state during the period of study in the hospital.

G. P., a woman aged 22, was first observed in October 1933. She had had pain radiating from the right hip to the leg for eight months prior to her admission, and for the past two months there had been blurring of vision. She presented few objective findings at the time of examination. The subjective complaints were those of a sciatic syndrome, and owing to the persistence of symptoms she received foreign protein therapy and epidural injections; on her discharge from the hospital there was slight improvement. The ocular findings were confusing, for there was also severe hyperopia. The blurred disks were regarded as suggestive of pseudoneuritis or of early papilledema. During this residence the cerebrospinal fluid was xanthochromic but was under normal pressure and showed no cells. After discharge the patient was at home for a time. The pain in the right lower extremity recurred; occasional headaches and failing vision developed, and she was readmitted to the hospital on Feb. 8, 1934, when she presented definite bilateral papilledema, questionable mimetic facial weakness on the right and hyperactive deep reflexes. None of the reflexes were pathologic, though the abdominal reflexes were depressed. She was fully conscious and

cooperative, and at this stage there was no vestige of the grasping phenomena. The spinal fluid was under a pressure of 240 mm.; it was turbid and xanthochromic and contained 974 red cells per cubic millimeter. An encephalogram revealed a large cyst in the left frontal region near the inner table of the frontal bone, with its lower surface near the roof of the orbit. On March 10, 1934, a tumor of the left frontal region, and with it the prefrontal area, was removed. Following the operation there was right hemiparesis. The mental picture varied; on days when she was semistuporous and seemed but partially aware of what was going on about her, a definite grasping occurred in the left hand, which persisted and became accentuated as long as the examiner's finger exerted pressure against hers. On the right side, however, which was paretic, there was no grasping phenomenon. On other days, when she was in deeper stupor and seemingly unaware of environmental stimuli, the grasping movements were not present.

Comment.—This case was one of extensive tumor of the left frontal lobe, with no grasping symptoms prior to operation when the patient was fully conscious. After extirpation of the tumor and the prefrontal area grasping movements occurred, not in the paretic right hand but in the apparently uninvolved left hand. Of greater interest are the observations that when fully conscious the patient showed no grasping movements, that none occurred when she was in deep stupor and that they were noted only when she was in that borderline stage between consciousness and unconsciousness.

COMMENT

Any attempt to analyze the mechanism underlying the production of the grasping phenomena meets with apparent contradictions that cannot be adequately explained. From available data, certain definite information is at hand. It has long been recognized that the human infant shows a grasping reflex for several months after birth and that this disappears when voluntary grasping begins and does not reappear except in the presence of disease of the frontal lobe.

The apparent implication that the volitional element inhibits the grasping phenomena has met with opposition from Walshe and Robertson.[17] These authors preferred to separate the movements into two groups: "grasping movements," to which they ascribed a volitional component, and "tonic innervation," which has a reflex component, is dependent on the proprioceptive stimulus of stretching and is entirely outside the patient's control.

Walshe and Robertson stressed the importance of the psychic condition of the patients in whom these movements occur. "They are, in fact, volitional movements occurring in individuals whose psychomotor functions have been reduced by disease of the brain to the production of the 'least voluntary' and 'most automatic' movements."

That clouding of consciousness plays an important rôle in the elicitation of the grasping phenomena also appears evident in a series of

observations on patients which Bender and Schilder [18] included in their studies on encephalopathia alcoholica. These patients, among other symptoms, showed grasping and groping. The comment of the authors on all the cases was that "with a clouding of consciousness, there always occur delirious features, together with grasping and groping. . . . It seems possible that these primitive tendencies come out when there is clouding of consciousness. In some way the clearness of consciousness seems to have an inhibitive effect."

The position of the body in space influences the grasp reflex. This has been described by Magnus in his studies on the righting reflexes.[19] When the animal lies in the lateral position, there is pronounced extension of the limbs on the lower side and flexion of those on the upper side. When the animal is turned over the pattern of response is reversed. Fulton [15] stressed the observation that when the animal is in the lateral position the grasp is well marked only in the extremities on the upper side. Thus, if the animal is on its right side, the left hand and left foot exhibit a vigorous grasp reflex. The right extremities show little or no grasping, provided the animal's head is reclining quietly on the table.

Magnus regarded this postural response as a body-righting reflex and stated that these changes persist in thalamic preparations after the labyrinth has been destroyed; he added that the postural response may be inhibited when the animal is in the lateral position by applying uniform pressure to the upper side of the body.

In his animals with lesions in areas 4 and 6 (animals with the motor and the premotor area removed from both hemispheres), Fulton described similar grasping phenomena and stated that uniform pressure applied to the upper side of the body inhibited the grasp.

Fulton described further how such a preparation acts when turned over rapidly. Rhythmic movements occur, similar to those shown by a dog or cat in attempting to right itself from the lateral position, while in the case of a monkey these rhythmic movements continue until the hand encounters a solid graspable object, when the rhythmic movements immediately cease and the body, by means of the grasp, tends to be pulled into the horizontal position.

In unilateral lesions the grasp may best be demonstrated if the animal lies in the lateral position with the involved side uppermost. These so-called righting reflex grasping phenomena suggest that apprehension and panic are important elements in the elicitation of the grasp. When the animal lies on the side, the under-side of the body feels secure; it

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18. Bender, L., and Schilder, P.: Encephalopathia Alcoholica, Arch. Neurol. & Psychiat. **29**:990 (May) 1933.

19. Magnus, R.: Körperstellung: Experimentell-physiologische Untersuchungen über die einzelnen bei der Körperstellung in Tätigkeit tretenden Reflexe, über ihr Zusammenwirkung und ihre Störungen, Berlin, Julius Springer, 1924.

is in contact with solid support, and the grasp is not present, while the upper side seeks something to preserve it—to cling to—and the grasp occurs.

Further, Fulton found that in monkeys with sections of the posterior nerve roots from the first cervical to the eighth dorsal, in which there was no grasp in response to stretching of the muscles, a sudden change of position caused the grasp to appear in the extremity, the afferent nerves of which were destroyed.

He concluded from these observations that "it is clear that the grasp is a fundamental part of the neurologic organization of the animal, since it can manifest itself in complete absence of the sensory innervation of the affected extremity."

SUMMARY

1. It is apparent that in certain pathologic states affecting cerebral activity grasping movements occur. These include:

(*a*) Flexion of the fingers into a grasp in response to tactile stimulation by any object or to that of stretching. The grasp persists as long as the stimulus continues.

(*b*) Pointing, grasping and groping movements of the hand in response to tactile or visual stimuli.

2. These phenomena are present when there is clouding of consciousness, irrespective of the site of the lesion. Drugs that act as cerebral depressants also induce the grasping reactions by causing marked reduction of responsiveness. During deep sleep induced by such a drug, no grasp movements are noted, but the movements occur before the animal falls asleep and again during the waking period. Similarly, in a case of a lesion of the frontal lobe, grasping was noted only when the patient was partly conscious, and then in the extremity not affected by the lesion. During full consciousness and in deep coma the grasp was absent.

3. The presence of grasping movements in states of panic and in experiments on the righting reflex suggests that fear plays an important rôle in the production of the grasping phenomena. In the righting reflex in animals the grasping phenomena occur only in the leg on the upper side, and this disappears when uniform pressure is exerted on the upper side of the body. This pressure may be regarded as allaying the animal's fear, when grasping ceases.

4. While lesions of the frontal lobe may cause grasping movements by producing clouding of consciousness, it is evident that grasping phenomena alone are not of specific value in localizing a lesion in the frontal lobe.

MENTAL SYMPTOMS IN CASES OF TUMOR OF THE FRONTAL LOBE

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The purpose of this investigation was to ascertain: (1) the frequency and nature of mental symptoms in cases of tumor involving the frontal lobe; (2) their diagnostic value as localizing symptoms and (3) whether there are any definite determining factors in their production.

The study was based on personal observations on eighty-five cases, in sixty-two of which the diagnosis was verified at necropsy and in

Location of Tumors and Their Histologic Structure

	Right Frontal Lobe	Left Frontal Lobe	Right and Left Frontal Lobes	Right Frontal Lobe and Adjacent Parts	Left Frontal Lobe and Adjacent Parts of Left Hemisphere	One or Both Frontal Lobes and Adjacent Parts of One or Both Hemispheres	Total Number of Cases
Number of cases	11	17	10	17	19	11	85
Glioma	4	9	2	15	14	9	53
Meningioma	3	6	8	2	4	1	24
Sarcoma	1	2	..	..	..	..	3
Vascular tumors (nonaneurysmal)	2	..	..	..	..	..	2
Tuberculoma	..	..	..	..	1	..	1
Carcinoma (metastatic)	..	..	..	..	..	1	1
Mesodermal tumor of unknown origin	1	..	..	..	..	..	1
Average duration of illness from appearance of tumor to death or to recovery following operation	21 mos.	21 mos.	19 mos.	19 mos.	17 mos.	12 mos.	18 mos.

twenty-three by operation. Seventy-five were observed in the neurologic service of the Mount Sinai Hospital and ten at the Montefiore Hospital. The location of the tumors and their histologic nature are shown in the accompanying table.

Abnormal mental reactions play an important rôle in the symptomatology of tumor of the frontal lobe. The reactions may occur at any time in the course of the disease. In many cases they are the earliest and in some the first symptoms of the disease, preceding by

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weeks, months or even years the neurologic evidences of an intracranial expanding lesion. Some patients with a tumor of the frontal lobe have a genuine psychosis, because of which they are admitted to a hospital for mental diseases, where the existence of an intracranial expanding lesion may not be recognized until necropsy. On the other hand, in patients with a definite psychosis of endogenous or exogenous etiology a tumor of the brain may develop in the course of the psychosis as an independent condition. A priori, one would expect the mental picture of a tumor of the brain to assume the characteristics of the so-called organic reaction type. Clinical experience, however, shows that this is not always the case.

Unusual difficulties may be encountered in the correct evaluation of the mental symptoms in a case of tumor of the frontal lobe, as in the case of brain tumors in other locations, in persons of advanced age who had cerebral arteriosclerosis prior to the appearance of symptoms and signs of a focal lesion in the brain. In such cases one must be guided solely by the history of the patient's previous mental condition. Ordinarily it is impossible to make an exhaustive and satisfactory investigation of the patient's personality prior to the appearance of the symptoms of brain tumor, especially with the patient in the state in which he usually is when he is hospitalized. It is obvious that it is not always safe to draw conclusions as to a patient's previous mental state from descriptions of behavior given by the average layman, as is frequently done in hospital practice.

Another disturbing factor in the evaluation of mental symptoms in cases of brain tumor is the frequent occurrence of the convulsive state. In many patients the abnormal mental state due to the presence of an intracranial growth may be wrongly interpreted and attributed to idiopathic epilepsy. As is well known, many patients with iodiopathic epilepsy are mentally backward; in others various abnormal mental states develop after the epilepsy has existed for a long time, and others show transient confusional states and various degrees of retardation in thought, speech and action from the prolonged use of sedatives administered for the seizures.

The actual determination of the presence or absence of mental symptoms may be difficult in some cases of brain tumor owing to disturbances in speech. The presence of motor or sensory aphasia, temporal anomia, apraxia or even dysarthria may so interfere with the patient's ability to communicate his thoughts to the examiner that the results obtained from the psychiatric examination are rendered difficult to interpret. In our material the data obtained from the psychiatric examination of aphasic patients was checked and rechecked because of the different interpretations given by the different examiners to the patient's answers, which were often made by gestures. The mental

capacity and the emotional state of most of these patients could be determined only by observing their reactions in the wards and by their mode of adjustment to the hospital routine. As a matter of fact, Marie and his school considered that every person with aphasia suffers from an intellectual defect—a view to which we do not fully subscribe.

We analyzed our material from the point of view of changes in personality, including disturbances in the sensorium, affect (including euphoria and facetiousness), memory and orientation, intellect and higher psychic functions, delusions, hallucinations, psychosexual symptoms and sphincteric disturbances.

Our method of approach in analyzing the various mental symptoms seemed to be the most feasible for our purposes. By employing this method we do not wish to imply that there exists a definite separation of the various psychic functions, for example, of intellect and emotion or of memory, intellect and emotion. We do not mean to revert to the old psychologic theory which conceived of mind as an aggregate of compartments into each of which, as White [1] said, "was pigeon-holed a special faculty such as feeling, thinking, and volition each one of which was considered distinct from the others." We fully realize that an abnormal mental state is the expression of an interference with the orderly functioning of the various mechanisms subserving the sensorium, association, projection and elaboration of sensory impressions, affect, memory and orientation, speech and intellect and the sum total of these, behavior.

A survey of the literature to discover the frequency of occurrence of an abnormal mental state in patients with tumor of the frontal lobe reveals that some authors reported such an abnormality in less than 70 per cent, whereas others found it in more than 90 per cent of their patients. Of our series, seventy-seven (over 90 per cent) showed at some time during the disease some abnormal mental reaction. In thirty-one (37.5 per cent) the mental symptoms were the earliest manifestations of tumor (charts 1 and 2).

DISTURBANCES OF THE SENSORIUM

Symptoms referable to disturbances of the sensorium leading to faulty perception and attention, poor concentration and lack of cooperation were the most frequent mental symptoms in our patients. Those symptoms were observed in sixty-one, or 71 per cent (charts 2 and 3). Normally the process of perception is dependent on sensations forcing their way into consciousness and arousing the engrams of former sensations. It is a complex reaction built up by reacting consciously to

1. White, William A.: Outlines of Psychiatry, ed. 3, Nervous and Mental Disease Publishing Co., 1911, p. 6.

visual, auditory, tactual and other sensory stimuli. For correct perception, therefore, it is essential that the sensory stimuli be of sufficient intensity, that the threshold of consciousness be adequate for the stimuli to cross it, that memory be intact and that the association mechanism

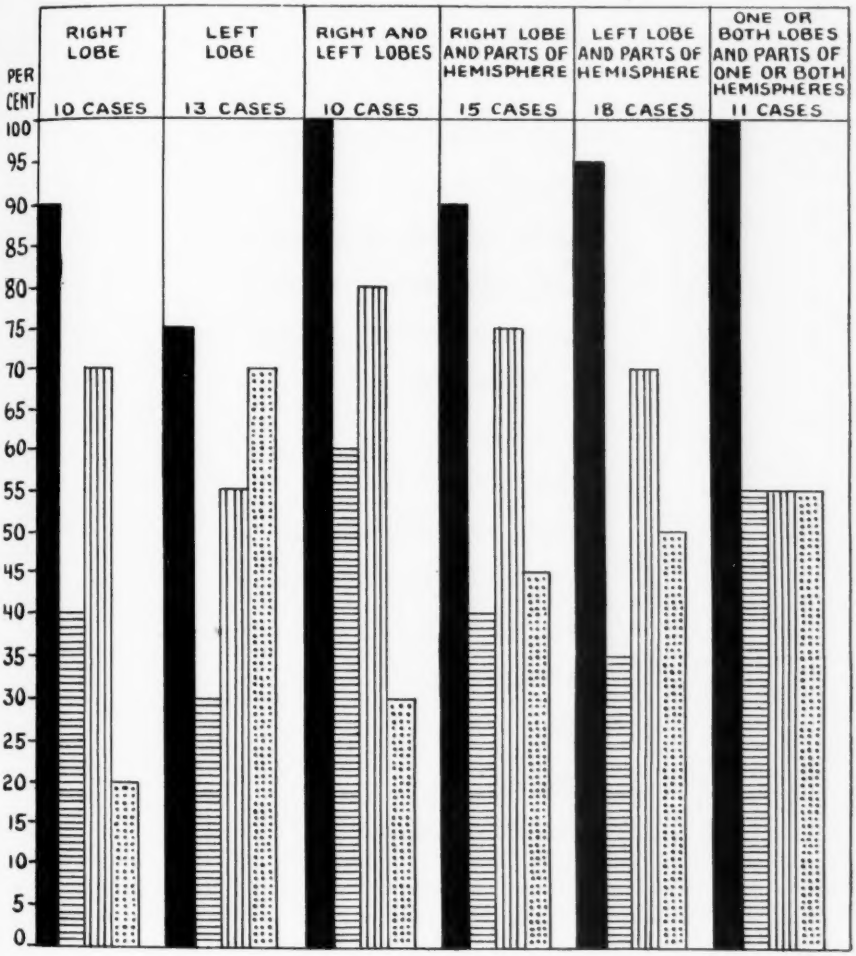

Chart 1.—The relationship of the mental symptoms, increased intracranial pressure and generalized convulsions in patients with tumor of the frontal lobe. The solid columns indicate the percentage of incidence of mental symptoms; the columns with horizontal lines, of the earliest manifestations; the columns with vertical lines, of increased intracranial pressure, and the columns with dots, of generalized convulsions.

be well integrated so as to enable the person to recall previous experiences and to associate them properly. A disturbance of consciousness leading to a heightening of its threshold must therefore result in dis-

turbed perception and attention. Disturbances of consciousness may vary from slight somnolence and drowsiness with frequent yawning to clouding of consciousness, stupor or coma.

Some authors have spoken of a peculiar kind of somnolence or stupor in cases of tumor of the frontal lobe (designated by Kennedy as "frontal stupor") from which the patient can be aroused only with great difficulty. According to Kennedy,[2] "this form of stupor is

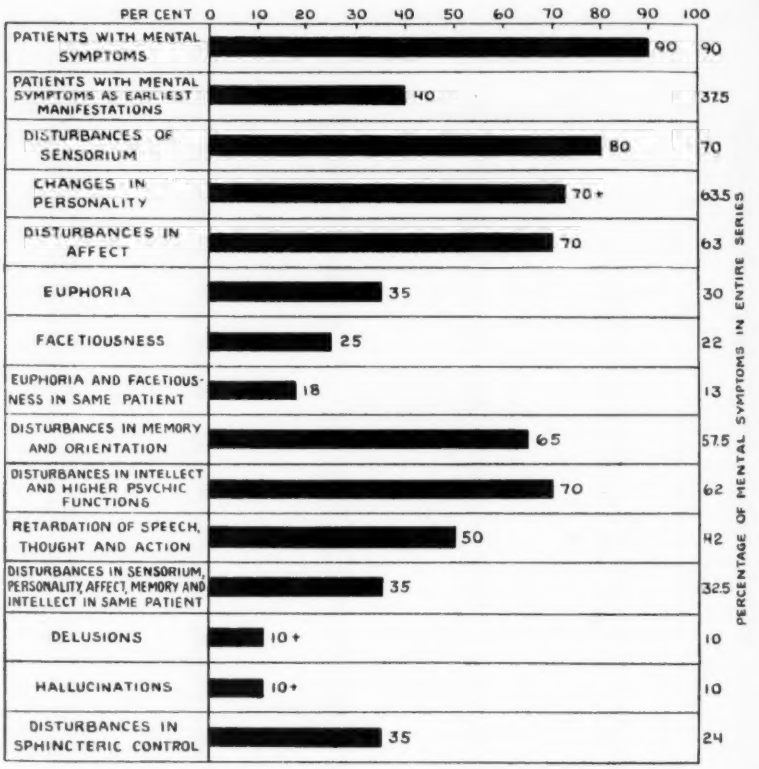

Chart 2.—The percentage of frequency of occurrence of mental symptoms in eighty-five cases of tumor of the frontal lobe. Mental symptoms were observed in seventy-seven cases.

hebephrenic and less profound than the morbid sleep due to lesions at the floor of the third ventricle as in lethargic encephalitis." Whereas in the case of the latter the patient may be aroused to crystal-clear consciousness, patients with frontal stupor when aroused by stimulation show merely a "turbid or muddled awareness." Although we have

2. Kennedy, Foster: The Symptomatology of Frontal and Temporosphenoidal Tumors, J. A. M. A. **98**:864 (March 12) 1932.

found Kennedy's criteria to be helpful in the differentiation of frontal lobe stupor or somnolence from that caused by lesions on the floor of the third ventricle, we do not believe that this type of stupor is pathognomonic of lesions of the frontal lobe because we have noted a similar state in patients with lesions in parts of the brain other than the frontal lobes.

Among the sixty-one patients with a disturbance of the sensorium there was evidence of increased intracranial pressure in forty-nine. The severity of the symptoms referable to disturbances in the sensorium was in direct relationship to the height of the intracranial pressure. Although our series includes patients with increased intracranial pressure in whom the sensorium was not affected and others in whom it was severely disturbed even though the intracranial pressure was normal or low, nevertheless increased intracranial pressure must be regarded as one of the most important determining factors in the frequency of occurrence and severity of symptoms referable to disturbances of the sensorium.

Among the sixty-one patients with a disturbance of the sensorium there were forty in whom the convulsive state was a prominent feature of the disease. Twenty-six of these presented generalized seizures, nine, both generalized and jacksonian seizures, and five, jacksonian attacks without loss of consciousness. Among the thirty-five patients who had generalized seizures with a loss of consciousness, there were fifteen in whom a disturbance in the sensorium affecting perception and attention preceded by weeks, months or even years the appearance of the first convulsive seizure; in the remaining twenty these symptoms appeared for the first time following a seizure or after several seizures had occurred. It is noteworthy that among the latter group were six in whom the evidence of disturbance of the sensorium, especially confusion, lasted much longer than is usually observed in patients with idiopathic epilepsy, whereas in the remaining fourteen the disturbances of the sensorium persisted and became more intense even in those in whom there was no recurrence of the convulsive state.

Our observations therefore show that more than two thirds of the patients with a disturbance of the sensorium were also subject to generalized convulsions. There apparently exists some relationship between the two types of manifestation, the precise nature of which we have been unable to determine.

Hallucinations.—These were noted in nine cases (chart 3); in one case their nature is not known; in one they were olfactory; in one gustatory; in four, visual, and in two, visual and auditory. In one of these the tumor involved the right temporal lobe in addition to the frontal lobe, and in one only the right frontal lobe was involved. A patient with a meningioma involving the right anterior and middle fossa had flashes before the eyes with blurred vision and heard bells

ringing. Whether these were hallucinations (visual and auditory) is difficult to say. This patient had no other mental symptoms but had 4 diopters of papilledema in each eye, diminished hearing on the right side, and diminished caloric responses on the right side.

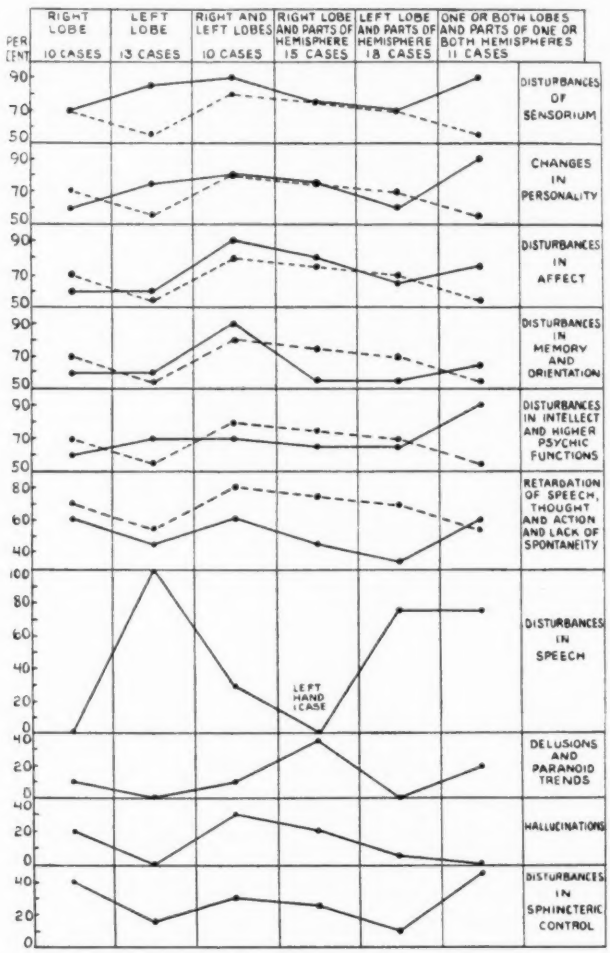

Chart 3.—The percentage of frequency of the occurrence of the principal mental symptoms. The solid line indicates the percentage of cases in which mental symptoms were observed, and the broken line indicates the percentage of cases in which intracranial pressure was present. One patient who had disturbances in speech, with a tumor in the right frontal lobe and the adjacent parts, was left-handed.

Two patients had a curious mental state allied to hallucination. One had, with complete retention of consciousness, clonic jacksonian seizures

affecting the right side of the face and the right upper extremity. Occasionally he had attacks during which he went into a "dream state," with partial motor aphasia but no convulsive phenomena and no loss of consciousness. The lesion found at operation was a meningioma embedded in the left frontoparietal region, bridging the sagittal sinus. In the other patient, the disease began seventeen months before admission with "uncinate phenomena" and "dream states." These consisted of episodes of olfactory hallucination lasting from two to three minutes two or three times a day, during which the patient "smelled horrible odors" which he was unable to identify. He also felt dizzy and "dreamy" and was "unable to utter words that his mind wanted to say but stood speechless till the attack passed off." Consciousness was not lost. These episodes appeared periodically for six months; then they suddenly ceased, and he began to have attacks of generalized convulsions with complete loss of consciousness. The lesion found at operation and necropsy was a meningioma compressing the cortex of the left frontotemporal region. It lay principally laterally and inferiorly to the left frontal lobe. The uncinate seizures in this case were probably due to compression of the left temporal lobe.

One patient had attacks of severe headache followed by a "cold feeling" of the left half of the body and "a metallic taste" in the mouth, which is a gustatory phenomenon. During these attacks he had generalized tonic convulsions lasting for a few minutes; consciousness was lost in only one of the attacks. At necropsy a meningioma the size of a hen's egg was found near the median longitudinal fissure, causing pressure on both frontal lobes but more on the left. The location of the tumor does not explain the gustatory phenomena in this case.

Neither the location of the tumor nor its nature was of significance with regard to the frequency of occurrence or the severity of disturbances in the sensorium. A determining factor of great significance, however, was the extent of the involvement. The more extensive the involvement, whether by the tumor itself or by secondary damage to the adjacent brain tissue, the greater were the frequency and severity of the disturbances of the sensorium leading to faulty perception, concentration and attention (chart 2).

It is evident, therefore, that the determining factors with regard to the frequency of occurrence and the severity of disturbances of the sensorium leading to faulty perception, concentration and attention are, in the order of their importance: (1) the extent of the involvement of brain substance by the tumor with secondary damage to the tissues adjacent to it; (2) increased intracranial pressure, and (3) possibly the convulsive state.

CHANGES IN PERSONALITY

A review of the literature reveals conflicting opinions as to the frequency of the various types of abnormal mental reaction in persons with a tumor of the frontal lobe. This is undoubtedly due to a lack of unanimity in interpretation and classification. This is especially noticeable in cases in which there was evidence of changes in personality. Thus, some authors attached the designation "changes in personality" only to changes in "mood," while others employed the same designation to connote changes referable only to the social aspects of personality. "Personality," according to Schwab,[3] "is the product of the play of psychic functions in and about the physical traits of differences." He therefore defined personality as "the projection into the external world of the inherent or acquired elements which make up the physical conformities of the individual organized into a composite picture through the synthetic action of consciousness." In studying our group with regard to changes in personality we considered that a patient was suffering from such changes whenever he showed a relatively persistent disturbance in psychosomatic integration sufficiently marked to impress those with whom he came in contact. We found a change in personality in 63.5 per cent of the patients (chart 2).

Whatever code one may employ in estimating a change of personality, if it is to be included as one of the symptoms of brain tumor as a criterion of localization it is essential to note the time at which such a change has occurred. When physical and mental deterioration have already occurred, a change in personality in a symptom complex of brain tumor is of no localizing value. On analyzing our material from this point of view we found eighteen cases (22 per cent) in which a change of personality was noted as one of the earliest manifestations of the intracranial growth.

It is noteworthy that in the cases in which the tumor involved both frontal lobes, or one or both frontal lobes and adjacent portions of one or both hemispheres, early changes in personality occurred much more frequently than in the cases in which the tumor was limited to one frontal lobe.

DISTURBANCES IN AFFECT

Symptoms referable to disturbances in affect were observed in fifty-four cases, or 63 per cent (chart 2). Unusual irritability was noted in twenty-three cases, in seven of which it was the first symptom and in three the only mental symptom throughout the course of the disease. Three patients were hypomanic (we have not included in this group those who were euphoric); two were "raging"; three were depressed, three were alternately exalted and depressed, and three were appre-

3. Schwab, S. T.: Brain **50**:480, 1927.

hensive. One had a typical manic-depressive reaction for which she had been sent to a hospital for mental diseases with the diagnosis of manic-depressive psychosis. Four were in a state of passivity but showed no evidences of intellectual enfeeblement, and seven were emotionally unstable, exhibiting varying affective reactions at different times.

Euphoria was present in 30 per cent of the patients, facetiousness in 22 per cent and both euphoria and facetiousness in 13 per cent (charts 2 and 4). One patient was euphoric only after convulsions; in two the euphoria did not appear until after a craniotomy, and in two it was the first symptom of tumor. In two patients facetiousness appeared for the first time after craniotomy. In contrast to the euphoria observed in the manic phases of the manic-depressive psychosis, the euphoria in patients with tumor of the frontal lobe is frequently associated with varying degrees of intellectual enfeeblement.

The greatest incidence of euphoria, facetiousness or both occurred in cases in which the tumor involved both frontal lobes. In this connection, however, it must be pointed out that this was also true for other symptoms (charts 4 and 5).

Pfeifer [4] long ago denied that euphoria and facetiousness were pathognomonic of disease of the frontal lobes. He reiterated his views in describing his experiences in the World War with sixty-four patients with gunshot wounds in the frontoparietal lobe (in twenty-nine the lesion was on the right side; in twenty-six, on the left, and in nine, bilateral). Euphoria was present in only four patients and facetiousness in one. Poppelreuter [5] could not find a patient with these symptoms among one hundred with injuries of the frontal lobe. These and other authors have expressed the belief that euphoria and facetiousness occurring with organic disease of the brain, regardless of its location, are merely an accentuation of the previous personality of the patient. We agree with this view even though, as we have stated, it is generally difficult to obtain reliable data as to the patient's personality prior to the onset of the symptoms of tumor. Euphoria and facetiousness have been observed by others as well as by ourselves in patients with tumor of the brain limited to the temporal lobes, with tumor of the third ventricle, with senile dementia, with cerebral arteriosclerosis and with other organic diseases of the brain, although no lesions were found in the frontal lobes.

We also studied the relation of the occurrence of these symptoms to involvement of the thalamus, but we could draw no definite conclusions. We are therefore inclined to regard euphoria and facetiousness as evi-

4. Pfeifer, Berthold: (*a*) Ueber psychische Störungen bei Hirntumoren, Arch. f. Psychiat. **47**:558, 1910; (*b*) in Lewandowsky, M.: Handbuch der Neurologie, Berlin, Julius Springer, 1923, vol. 1, p. 510.

5. Poppelreuter, cited by Pfeifer.[3b]

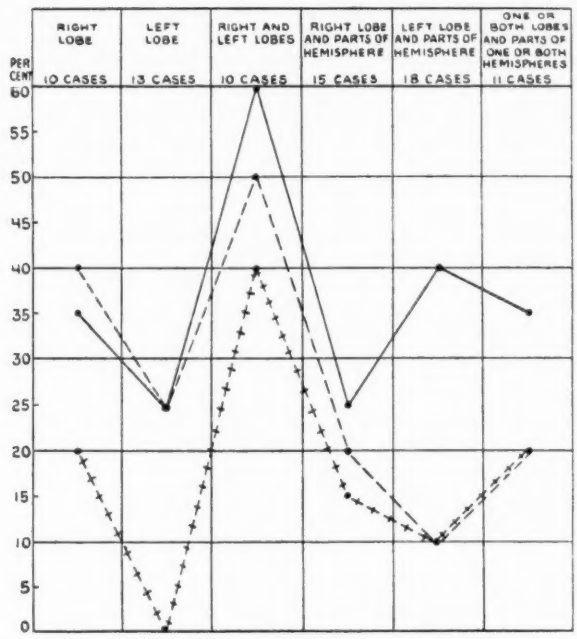

Chart 4.—The percentage of frequency of occurrence of euphoria and facetiousness. The solid line indicates the cases in which euphoria was observed; the broken line, the cases in which facetiousness appeared, and the cross-hatched line, the cases in which both euphoria and facetiousness appeared.

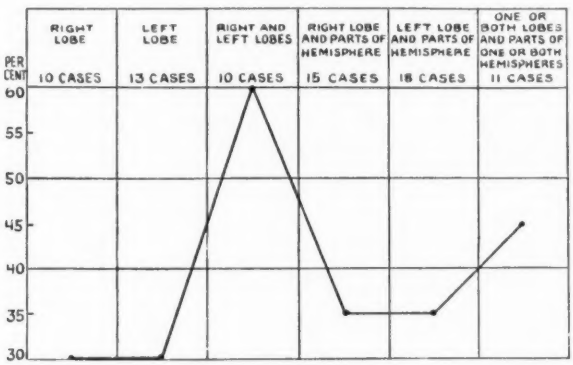

Chart 5.—The percentage of frequency of disturbances in sensorium, personality, affect, memory and intellect in the same patient.

dences of diminution or loss of cortical inhibition, which may occur with lesions of the brain regardless of their location.

Various attempts have been made to formulate a mental symptom complex characteristic of tumor of the frontal lobe. The essential features of this symptom complex are said to be a change in personality and a peculiar disturbance in affect, characterized by a subjective feeling of well-being, or euphoria, associated with a tendency to facetiousness, joking and punning (*moria* or *Witzelsucht*), with lack of insight into, or indifference to, the actual condition. In our entire series we could find only two patients in whom all the features of this symptom complex were present.

For a symptom to be of localizing value one would expect the incidence to be much greater than it was in our patients, among whom euphoria was present in 30 per cent and facetiousness in 22 per cent (charts 2 and 4). We therefore do not believe that euphoria and facetiousness by themselves are pathognomonic of tumor of the frontal lobe although they assume considerable localizing significance when taken in conjunction with other signs and symptoms pointing to involvement of the frontal lobes.

DISTURBANCES IN MEMORY AND ORIENTATION

Disturbances in memory and orientation are psychologically so closely related that in some cases it may be impossible to distinguish them. Memory and orientation are complicated psychic functions depending on several factors: the will to remember, to retain and to recall; the affective state in which the person is when the various stimuli destined to become memory impressions enter consciousness, and the intactness of the mechanisms of association and projection.

Disturbances in memory and orientation were present in 65 per cent of the patients with mental symptoms and in 57.5 per cent of the entire series (charts 2 and 3). In eight cases they were the earliest manifestations of an intracranial lesion, and in two they were present only during the confusional state following convulsive seizures. In four cases they appeared for the first time and became permanent after craniotomy or after intracranial injections of air. In five cases a coexisting temporal anomia made it impossible to determine definitely whether there was also present an actual memory defect, although judging from the patients' behavior in the ward such a defect was thought to exist. Three patients in the seventh decade of life had marked disturbance in memory and in orientation, but the factor of age cast considerable doubt as to whether the disturbances were due to the tumor, although careful inquiry of relatives failed to elicit any history of a disturbance of memory prior to the appearance of evidence of an expanding intracranial lesion. We could find no instance of a Korsakoff psychosis in our series.

We mention this because continental psychiatrists have reported the occurrence of the Korsakoff syndrome in patients with tumor and injury of the frontal lobe.

Many authors have stated that in lesions of the frontal lobe the disturbances of memory are particularly marked for recent events, whereas the memory for past events may remain unimpaired. This is known as Ribot's law, which is held by most writers to be applicable to disturbances of memory occurring in any disease of the brain. Alexander has recently shown that this law is not well founded. In all cases in which there is a disturbance in memory, the memory of recent events is mostly affected, because in such cases there is almost always a coexisting disturbance in consciousness, perception, attention and concentration, as a result of which recent events and stimuli either do not enter consciousness or, if they do enter it, do not remain long enough to make a psychic impression of sufficient intensity to be recalled; i. e., amnesia occurs by faulty fixation. This differentiation, therefore, is of no diagnostic value.

In twenty-eight of forty-seven patients with disturbance of memory and orientation there were definite evidences of increased intracranial pressure; in the remaining nineteen no such relationship could be established. Although our series includes fourteen patients in whom there was marked increase of intracranial pressure and who showed no evidence of disturbances in memory and orientation, nevertheless one is justified in assuming that increased intracranial pressure is a factor of considerable importance in determining the occurrence of disturbances referable to the complex function of memory.

Our observations seem to show that the occurrence of disturbances in memory and orientation bears no relation to the location of the tumor but is associated rather with the degree of the intracranial pressure and the extent of involvement of the brain substance. These symptoms, therefore, are of no localizing value and are regarded as general symptoms of brain tumor, indicative of interference with the general activity of the brain, which may be due to various causes, of which increased intracranial pressure seems to be the most important and the extent of involvement next in importance.

DISTURBANCES IN INTELLECT AND HIGHER PSYCHIC FUNCTIONS

Symptoms referable to disturbances in intellect and the higher psychic functions were found in 70 per cent of the patients with mental symptoms and in 62 per cent of the entire group (charts 2 and 3). The disturbances in the intellectual sphere were manifested chiefly by a diminution or loss of the capacity to synthesize simple thought processes into more complex thinking. The defective thinking in these patients was apparently not due to a primary poverty of ideas, as in persons

with congenital mental deficiency, but to an inability to perceive impressions correctly, to construct ideas from these impressions, to associate and integrate them and finally to rationalize regarding them so as to reach certain judgments which would eventually lead to proper action. It is obvious that this complex process cannot be performed adequately by a person suffering from disturbances in any of the elemental components of consciousness, in memory and orientation, in affect or in all of these. A survey of our material reveals that almost all patients who had symptoms referable to disturbances of intellect and of the higher psychic functions also had symptoms referable to disturbances of the sensorium, memory and affect. In most cases the former did not appear until the latter had been in existence for some time.

In some cases the disturbance of intellect was manifested only by retardation in thinking and by a slowness in the elaboration of ideas leading to difficulties in reaching conclusions and forming judgments. As the disease advanced there was noted a gradual merging from mere retardation of thinking to intellectual deterioration, leading finally to total paralysis of thought and abeyance of all the higher psychic functions.

Nine patients showed a peculiar disinterestedness and indifference characterized by a failure to realize the seriousness of their condition. In most instances it was difficult to determine whether this indifference was due to a "frozen" affect or to poor judgment.

Mental retardation is frequently mentioned as one of the pathognomonic symptoms of tumor of the frontal lobe. A critical analysis of the cases on which this assertion is based leaves the reader in doubt as to the precise meaning attached by those reporting such cases to the designation "mental retardation." Authors seem to employ this term to designate variously: slow cerebration; mental dulness; psychomotor retardation; slowness of speech, thought and action; poverty of ideation; catatonic states, and cerebral inhibition. In our series, mental retardation was present in 42 per cent of the patients (charts 2 and 3). We encountered insurmountable obstacles in our attempts to analyze our material with a view to determining how many patients were actually suffering from retardation. In the first place, the patients with complete and even those with partial aphasia were slow to comprehend and to speak and appeared superficially to be suffering from slow cerebration. Patients with disturbances of the sensorium and affect (the depressed) certainly appeared to be retarded. It is obvious that patients with hemiplegia or even with hemiparesis were all slow, if not in thought, certainly in action. Others, even though they showed no disturbances in speech, motility or sensation, were suffering from such severe headache or weakness from vomiting and general exhaustion that they appeared to be retarded in every sphere.

Some of our patients showed a lack of motor spontaneity before there were evidences of disturbances of the sensorium, affect and personality. This lack was especially striking in speech, even in cases of tumor of the right frontal lobe in right-handed persons. The lack of spontaneity in thought, action and speech resembled the hypokinesia and akinesia described by Kleist, Pfeifer, Cramer, Foerster, Heilig, Berger and others in cases of gunshot wounds of the frontal lobes.[6] Most of these authors expressed the belief that the prefrontal region contains a center regulating the speed of movement, the destruction of which produces a diminution of spontaneity and rapidity of movement. Poppelreuter did not agree with this view. In our patients with lack of spontaneity and diminution of speed of thought and action, the prefrontal areas were not always involved by the tumor or by any secondary reactive phenomena. In our opinion, retardation by itself is no more pathognomonic of involvement of the frontal lobe than it is of involvement of any other part of the brain or of any other debilitating disease.

In recent years we have been subjecting some of our patients with brain tumor to psychometric investigations. These revealed that most of the patients showed varying degrees of intellectual deterioration in the later stages of the disease, regardless of the location of the tumor. The degree of intellectual deterioration was in direct proportion to the rapidity and extent of the growth as well as to the number and severity of the mental symptoms referable to the other psychic spheres. We also found that the degree of intellectual deterioration bore a noticeable relationship to the degree of intracranial pressure. When the latter was reduced, the abnormal mental picture would show marked improvement which would persist as long as the intracranial pressure remained low.

DELUSIONS

Delusions are recorded in 10 per cent of the cases (charts 2 and 3). In one patient they appeared for the first time following craniotomy. Another patient, a woman with a metastatic carcinoma (from a bronchus) in the left frontal lobe and another metastasis in the pons, had ideas of reference and was delusional for two years before there developed signs and symptoms of focal brain disease. She had no other mental symptoms until some months before death when she began to show evidences of profound mental deterioration.

It is noteworthy that in all patients with delusions the tumor was extensive. In one it was limited to the right frontal lobe, in another to both frontal lobes, and in the remaining seven it involved the frontal

6. Lewandowsky, M.: Handbuch der Neurologie, Berlin, Julius Springer, 1923, vol. 1, p. 510.

and adjacent lobes. There was nothing in the content of the delusions that could be associated with the existence of a brain tumor, except in a case of a spongioblastoma which occupied almost the entire right frontal lobe, in which the patient insisted that she had an egg in her head which she hoped happy Hooligan would soon remove. The delusions in the other cases were of the type usually observed in cases of toxic states and of organic disease of the brain from causes other than tumor. They were most likely expressions of an abnormal mental make-up that came to the surface under the stimulus of an abnormally functioning brain.

DISTURBANCES IN THE PSYCHOSEXUAL SPHERE

Psychosexual disturbances were recorded in five cases.

One patient was an unmarried woman, aged 63, who, although she had very severe headache and seemed to be very ill, was nevertheless coquettish and showed evidences of eroticism. Throughout her stay in the hospital she expressed a preference for examinations by the male members of the hospital staff, with whom she would cooperate much better than with her regular ward physician, who happened to be a woman. The tumor was a large spongioblastoma in the right frontal lobe.

A woman, aged 28, who had been separated from her husband before the onset of the illness, showed slight confusion, marked facetiousness and flirtatiousness. The facetiousness was characterized by jokes which invariably had a sexual content. The tumor was a large spongioblastoma in the middle and inferior portions of the posterior part of the left frontal lobe.

A man, aged 42, suddenly underwent a change in disposition. He became moody, spoke little and lost sexual desire completely. The tumor was a glioma, 4 by 4 by 7 cm., situated wholly in the mesial half of the left frontal lobe.

One patient lost libido six months before admission, when the disease was already well established; this was about three and one-half years after the onset of the illness. Here the loss of libido was a relatively late symptom. The lesion was a very large "hemangiomatous" endothelioma attached to the falx cerebri and longitudinal sinus, which had indented the left prefrontal area and the parietal and temporal lobes.

A man, aged 43, masturbated in the presence of his wife and her women friends early in the disease, which began with drowsiness and rapid intellectual deterioration. The tumor (a spongioblastoma) involved both frontal lobes, the right temporal lobe, the left internal capsule and the brain stem.

SPHINCTERIC DISTURBANCES

Sphincteric disturbances, not including those occurring during the convulsive state, were recorded in 24 per cent of the cases (charts 2 and 3). In three, urinary incontinence was among the earliest symptoms of the disease and was probably due to the marked disturbances of the sensorium which the patients showed. In the remaining cases the incontinence was a late symptom and was due to intellectual enfeeblement and general dilapidation. Incontinence was present in twenty cases; four of the patients had only urinary and sixteen both urinary and fecal incontinence. One patient with a spongioblastoma which infiltrated the right frontoparieto-occipital lobe had urinary retention three months after the onset of the illness and long before there were any disturbances of the sensorium or intellect. We are unable to explain the retention in this case.

Incontinence was present in six of twenty-seven cases (22 per cent) in which the tumor was limited exclusively to one frontal lobe; in three of ten (33 per cent) in which the tumor involved both frontal lobes, and in eleven of forty-six (24 per cent) in which the tumor involved one or both frontal lobes and in addition adjacent structures in one or both hemispheres (chart 3).

There is apparently no direct relationship between the occurrence of incontinence and the extent of brain substance involved by the tumor. On the other hand, a correlation of the occurrence of incontinence with the degree of intracranial pressure shows that increased pressure, by producing disturbances of the sensorium (drowsiness and stupor), is an important determining factor in the production of incontinence. A small tumor, therefore, located so as to interfere with the intracranial circulation of the cerebrospinal fluid is more apt to give rise to incontinence than a large tumor which is infiltrating and does not produce increased intracranial pressure.

The site of the cortical centers for sphincteric control in man has not as yet been definitely established. It is thought by some to be in the motor region between the arm and the leg center, or in the hip region, and by others to be in the paracentral lobule. In our series there were only five cases of incontinence in which there was involvement of the parietal lobe in addition to that of the frontal lobe. On the other hand, there were several cases in which the tumor involved the frontal and parietal lobes and the patient was not incontinent.

There is some clinical as well as experimental evidence that, in addition to the centers in the cerebral cortex and those in the lower portion of the spinal cord, there exist subcortical centers (in the basal ganglia) for sphincteric control. A pathologic process at any of those levels may interfere with normal sphincteric control. It is well known that sphincteric disturbances are rarely observed in a unilateral patho-

logic process, whether it is in the cortex, in the basal ganglia or in the cord. Although the occurrence of sphincteric disturbances in cases of bilateral involvement could be explained on anatomic grounds, their presence in cases of unilateral involvement cannot be attributed to the site of the pathologic process. It is also noteworthy that these disturbances were present in some cases in which the tumor was small and encapsulated. It is therefore most likely that disturbances in sphincteric control are an expression of the abnormal psychic state of the patients, and as such they assume the rôle of a general symptom of brain tumor. Of the patients with incontinence, all but two died. Incontinence, therefore, may be of some significance as a bad prognostic sign in cases of tumor of the brain.

PATHOGENESIS OF MENTAL SYMPTOMS IN CASES OF TUMOR OF THE FRONTAL LOBE

There is no unanimity of opinion as to the pathogenesis of the abnormal mental states observed in cases of brain tumor. In patients with a familial or hereditary predisposition to mental disease the tumor itself may be the precipitating cause. In others, even without a predisposition, the tumor may be the cause of the mental symptoms. Favoring this theory is the fact that in some cases the mental symptoms disappear following extirpation or even partial removal of the tumor. On the other hand, cases are encountered in which the mental symptoms persist even though the tumor has been entirely removed.

It is hardly likely that the size of the tumor is the sole determining factor in the development of the mental symptoms. Very large tumors may exist for years without causing the slightest evidence of mental disturbance, whereas small tumors, even though they do not impinge on the ventricular system or cortex, may give rise to abnormal mental states resembling, in some instances, true psychoses.

In some cases the mental symptoms disappear for a considerable period after a mere decompression or repeated lumbar, ventricular or cisternal puncture or the intravenous administration of hypertonic solutions. It seems, therefore, that in such cases increased intracranial pressure is the necessary additional factor in the production of mental symptoms. Increased intracranial pressure by itself, however, is not the sole determining factor in the genesis of the mental symptoms, because mental symptoms occur in many cases of brain tumor in which there is no evidence of increased intracranial pressure, whereas in other cases in which there is increased intracranial pressure the entire course may be run without the appearance of mental symptoms. In this connection it may be pointed out that in cases of infratentorial tumor mental symptoms are much less common than in cases of supratentorial lesion,

although infratentorial tumors are as a rule associated with much higher intracranial pressure than are supratentorial tumors.

Another factor that may play a determining rôle in the production of mental symptoms is the circulatory disturbance in the brain tissue adjacent to the tumor, due to direct compression of the blood vessels by the tumor followed by secondary softening. Circulatory disturbances in the brain may also occur in regions remote from the tumor.

Finally, it is thought by some that toxic material produced by the degeneration of the tumor tissue and by the disintegration of adjacent brain tissue is absorbed into the circulation and gives rise to mental symptoms. While this possibility cannot be denied, no satisfactory evidence has yet been advanced in support of the theory.

In the present state of knowledge it is impossible to attribute the pathogenesis of the mental symptoms in cases of brain tumor to any one factor. It is more likely, as we have stated, that there are several factors at their basis, even though we do not know the precise rôle played by any of them. From a statistical point of view the most significant of these factors are the location of the tumor (supratentorial or infratentorial), the extent of involvement (size of the tumor), the changes in the adjacent brain tissues, and the increased intracranial pressure. The significance of the location of the tumor is obvious when one takes into consideration the fact that mental symptoms are much more frequent in cases of supratentorial than in those of infratentorial tumor and that in the latter, mental symptoms occur only when, as a result of internal hydrocephalus, normal functioning of the cerebral hemisphere becomes disturbed. In other words, the mental symptoms in these cases are really indirect symptoms. Conditions are different in cases of supratentorial tumor, especially in cases of tumor of the frontal lobes. The frontal lobes are connected with every other part of the brain; they have important association connection with the parietal, temporal and occipital lobes, as well as with the cerebellum. It is obvious, therefore, that involvement of the frontal lobes which is sufficiently severe to affect these association tracts will give rise to various forms of abnormal mental states. It must also be pointed out that in attempting to correlate the frequency of occurrence and the various types of abnormal mental reactions in our patients with the anatomic location of the lesions we found that the actual site of the tumor (cortical or subcortical, frontal, prefrontal or subfrontal) was not a determining factor.

CONCLUSIONS

1. Abnormal mental reactions occurred in seventy-seven of our cases (over 90 per cent) at some time during the course of the disease.

2. Mental symptoms were the earliest manifestations of tumor in 43 per cent and changes in personality in over 30 per cent of the cases.

3. Symptoms referable to disturbances of the sensorium were most common; next in the order of frequency were changes in personality and disturbances in affect, intellect, memory and orientation.

4. Euphoria was present in 30 per cent, facetiousness in 22 per cent and both in 13 per cent of the cases. Euphoria and facetiousness, especially the latter, do not occur with sufficient frequency to justify their consideration as pathognomonic of tumor of the frontal lobe. They are most likely exaggerated expressions of the patient's previous emotional state.

5. The actual part of the frontal lobe involved by the tumor, i. e., whether cortical, subcortical, premotor, prefrontal or subfrontal, cannot be regarded as a determining factor in the frequency of occurrence of mental symptoms or in their nature.

6. Determining factors in the frequency of occurrence, nature and severity of mental symptoms are, in the order of their importance, as follows: (1) the extent of involvement (direct or indirect) of the brain tissue; (2) the rapidity of growth of the tumor; (3) the increased intracranial pressure; (4) the patient's previous mental make-up, and (5) possibly the convulsive state.

7. In cases of rapidly growing infiltrating tumors and of diffuse tumors mental deterioration and changes in personality appear much earlier than in cases of slowly growing tumors; in the latter, changes in personality may for a long time be the only mental symptom.

8. Increased intracranial pressure is an important determining factor in the production of disturbances of the sensorium and of spontaneity of thought, action and speech.

9. There is no noteworthy difference in the frequency of occurrence of, and in the nature of the mental symptoms caused by, tumors of the right hemisphere and of the left.

10. By themselves, mental symptoms are of little value in the diagnosis of a tumor of the frontal lobe. Mental pictures indistinguishable from those found in our patients with tumor of the frontal lobe occur also in aged and arteriosclerotic patients and in patients with other organic diseases of the brain, regardless of their location.

DISCUSSION

Dr. Foster Kennedy, New York: I was a little surprised at Dr. Keschner's conclusions. He seemed to show by the whole of his paper that mental symptoms occurring early in the life history of the brain tumor were indicative of a frontal lobe localization and his concluding remark was that they were *not* of diagnostic value. That seems like a contradiction in terms, for I thought that his paper showed that changes in personality, particularly retardation of thought, instances of thought block, occurred early in the disease and if one is sure that a brain tumor is present and finds that such conditions have occurred in personality and in the

working of the mind, I think it is of important diagnostic value in determining the position of the tumor.

Of course, if one does not know that a tumor exists, then one is naturally in a position in which such changes of personality are of no localizing value. If one knows the tumor is present and early personality changes occur, I believe that one has authority for believing that the tumor is located in the frontal lobe. The absence of hallucinations in frontal lobe tumors has always been interesting to me in contrast to their frequency in temporosphenoidal lesions.

I think Dr. Keschner and Dr. Strauss found inapt jocosity was less common than the books would have us suppose. That has not been exactly my experience, perhaps because I was impressed early by its frequency and looked for it and awaited its presence more than it deserves. I believe there is evidence in these cases, as contrasted with the absence of mental symptoms in tumor of other parts of the brain, for believing in the old doctrine of an intellectual orientation in the frontal lobe.

Dr. Emanuel D. Friedman, New York: Would Dr. Keschner be good enough to tell us whether he found any difference in the incidence of mental symptoms in meningiomas and in gliomas?

Dr. Irving J. Sands, New York: It is obvious that the limitation of time has prevented the doctor from thoroughly presenting his topic, and I am therefore looking forward with a good deal of pleasure to reading this valuable paper when published. As I recall the cases of psychosis with brain tumor that came to necropsy in Ward's Island from 1917 to 1920, when I was associated with the pathologic department of that institution, the thing that impressed itself on me was the bilaterality of the involvement of the brain by the tumor.

It has been my experience that the gliomas cause more profound mental changes than do the endotheliomas. I have the impression that tumors involving the upper portion of the frontal lobes, and particularly those that involve the white matter as well as the gray, cause greater psychic changes than those that occur on the lower surface of the brain and involve the gray matter only.

Dr. Richard M. Brickner, New York: The question of bilaterality of involvement of the frontal lobes, raised by Dr. Sands, is of special interest. The literature indicates that mental symptoms occur only when both lobes are involved, either directly or indirectly. I should like to learn more distinctly what the authors thought of that point. In cases of very small tumors, limited to one lobe, when there could hardly have been much direct pressure on the opposite lobe, were there psychic symptoms?

It is also interesting that there was so little vesical incontinence, a symptom which appears to be among the most characteristic of frontal lobe tumors.

Dr. Bernard J. Alpers, Philadelphia: Is there any difference with involvement of the corpus callosum and are the symptoms different and in what way do they differ from the symptoms when there is involvement of only the frontal lobe?

Dr. Moses Keschner: Our conclusion as regards the pathognomonicity of mental symptoms in frontal lobe tumor does not differ essentially from that of Dr. Kennedy. We state in our paper that *by themselves* mental symptoms are of little value in the diagnosis of frontal lobe tumor because mental pictures indistinguishable from those found in our cases of frontal lobe tumor occur also in aged, arteriosclerotic persons and in other organic diseases of the brain regardless of their location.

As regards euphoria and facetiousness: Dr. Strauss and I believe that euphoria and facetiousness may be more frequent in tumors of the frontal lobe than we

actually found, but, of course, our conclusions had to be based on our figures, which speak for themselves.

As to the difference in the mental symptoms produced by the meningiomas and the gliomas, we found that in the glioma group, especially in the spongioblastomas, mental deterioration and changes in personality occur much earlier than in the meningiomas; in the latter changes in personality may for a long time be the only mental abnormality.

We could not find any definite correlation of the mental symptom complex with the localizations of the tumor; it made no difference whether the tumor was located cortically or subcortically, or whether it was premotor, prefrontal or subfrontal in location.

As regards the mental symptoms in bilateral involvement by the tumor we wish to say that our graphs show definitely that mental symptoms were present in every case with bilateral involvement.

As to the vesical incontinence: Twenty-four per cent of our patients showed vesical incontinence; it was most frequent and most marked in the cases in which both frontal lobes were affected and in those in which the lesion involved one or both frontal lobes and the adjacent hemisphere on one or both sides.

As regards mental symptoms in the cases in which the corpus callosum was involved: We found in our cases that when the corpus callosum was involved by the tumor directly or indirectly, there was also marked involvement of one or both frontal lobes and the adjacent portions of the cerebral hemispheres. It was impossible, therefore, to determine precisely which component of the mental symptom-complex was due to the involvement of the corpus callosum and which to that of the rest of the brain. The general impression we gained, however, was that there was no difference which could be utilized as a diagnostic criterion of involvement of the corpus callosum, at least as far as mental symptoms were concerned.

DEMENTIA PARALYTICA

RESULTS OF TREATMENT WITH MALARIA IN ASSOCIATION WITH OTHER FORMS OF THERAPY

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This is the seventeenth year since the original communication of Wagner von Jauregg on the treatment of dementia paralytica with malaria fever. In the course of these seventeen years many reports have accumulated from all over the world on this use of malaria; almost without exception the reports have been favorable. Therefore, it seems justifiable to state that malaria has a distinctly beneficial effect on patients suffering from dementia paralytica.

The questions that remain to be considered are: How favorable are the results to be obtained and what are the best methods? The present communication deals with a series of patients treated at the Boston Psychopathic Hospital between February 1925 and February 1931, analyzing the results of treatment in the year 1934. The common factor in the treatment was malaria, although other treatment may have been given prior to or subsequent to the treatment with malaria. This group of cases and the results obtained are, therefore, not exactly comparable with other series reported by other authors. In fact, there are hardly two groups reported in the literature that are comparable with each other; many variants enter, such as the type of treatment given, the selection of patients (varying from those in whom the condition is mild and is in an early stage to others in whom it is advanced and late) and the length of time that the patients were followed before the report was made, not to mention the personal equation which enters into the conclusions reached. As one goes through the reports one is struck by the fact that the majority of them are incomplete as regards many factors required for a careful and satisfactory summary.

Our reason for reporting this series of 173 cases is that we believe that they have been, on the whole, carefully followed over a period of

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From the Boston Psychopathic Hospital.

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years and that the results represent a moderately exact summary of what has been accomplished in a reasonably large group.

Moore,[1] on the basis of an analysis of 5,000 cases reported in the literature, including all types, both early and advanced, found that a complete remission was recorded in 25 per cent; an incomplete remission but with the ability to work, in 20 per cent; an incomplete remission requiring permanent hospitalization, in 25 per cent; no improvement, in 20 per cent, and death during or shortly after treatment, in 10 per cent. In the mass statistics given by Moore, made up from series of cases varying from a small number to several hundred, the results vary greatly. An excellent summary of the cases reported in the literature up to 1926 was given by Ferraro and Fong,[2] who recorded the

TABLE 1.—*Results of Malarial Therapy in Cases of Dementia Paralytica Reported in the Literature*

Author	Number of Cases	Percentage of Good Remissions	Percentage of Partial Remissions
Reece and Peter (1924), cited by Ferraro and Fong [2]	236	20.0	50.6
Jossman and Steenarts (1924), cited by Ferraro and Fong [2]	100	21.0	28.0
Gerstmann (1925), cited by Ferraro and Fong [2]	400	33.0	14.2
Nonne (1925), cited by Ferraro and Fong [2]	450	30.0	....
Ferraro and Fong [2]	120	25.75	27.39
Matz: J. Nerv. & Ment. Dis. **68**: 113, 1928	346	23.99	41.04
O'Leary, P. A.: Treatment of Neurosyphilis by Malaria, J. A. M. A. **91**: 543 (Aug. 15) 1928	57	41.0	24.0
Bennett, Polozkes and Altshuler: J. Michigan M. Soc. **28**: 241, 1929	278	33.0	....
Warner [5]	131	40.5	....
Paulian: Rev. neurol. **1**: 1166, 1929	155	30.4	34.1
Haskins: Psychiat. Quart. **5**: 733, 1931	100	33.0	....
Stanley: Psychiat. Quart. **6**: 310, 1931	181	29.7	8.2
Hinsie and Blalock [3]	105	21.0	19.0
Moore [1]	500	35.0	43.0

results in sixty-four series from clinics all over the world. The number of cases in each series, as summarized in this article, varies from a low figure of 3 to 400 cases reported by Gerstmann in 1925 and 450 cases reported by Nonne in the same year. Likewise, there is a marked difference in the percentage of good remissions reported, varying from a low figure, 8.21 per cent, given by H. and A. McIntyre in 1926 in a series of 40 cases, to a high percentage, 62.4, in a series of 19 cases reported by Grafe in 1923 and an even higher percentage, 68, reported by Weygandt in 1922 (Weygandt, however, gave no indication of the number of patients treated).

1. Moore, J. E.: The Modern Treatment of Syphilis, Springfield, Ill., Charles C. Thomas, Publisher, 1933, p. 405.

2. Ferraro, A., and Fong, T. C.: Malaria Treatment in General Paresis, J. Nerv. & Ment. Dis. **65**:225 (March) 1927.

Table 1 gives in tabular form the reports of several of the larger series, showing a good remission in from 20 to 41 per cent of the cases and a partial remission in from 8.2 to 50.6 per cent.

MATERIAL AND METHOD OF ANALYSIS

The material which we present consists of data on the cases of 173 patients with dementia paralytica treated at the Boston Psychopathic Hospital. In each case the diagnosis was made on the basis of clinical studies and observations on the spinal fluid, it being held requisite for the diagnosis that the spinal fluid give the typical strong reaction characteristic of the disorder.

We wish to emphasize that this material is somewhat selective. In many of the patients entering the Psychopathic Hospital the disease is in a rather early stage, and because of limited bed space a selection of the patients entering the hospital is necessary; on the whole, those in whom the disease was in the earlier periods and who were in fairly good physical condition were chosen. It must also be recorded that a few patients had had a considerable amount of treatment prior to the treatment with malaria. Malarial treatment was given to these patients after other treatment either because they were not progressing satisfactorily from the clinical or the serologic standpoint or because they were anxious to have the benefit of malarial as well as of other types of treatment.

The group of 173 patients was made up of all patients to whom we gave malarial treatment between February 1925 and February 1931, and the results were analyzed as of February 1934. Therefore, in the case of patients who received treatment in the year 1925-1926, between eight and nine years elapsed from the time the treatment was given to the time of the analysis, whereas the shortest period in which the patients were studied after the treatment was three years.

The results of the treatment are analyzed from two points of view: (1) the clinical status of the patient and (2) the observations on the spinal fluid. It is, of course, extremely difficult to evaluate clinical results properly when one is dealing with matters of conduct, judgment and the finer components of the personality, which are what one has to consider in cases of dementia paralytica. We have attempted to make this analysis, but we realize that the conclusions concerning the clinical improvement of patients with dementia paralytica are always open to suspicion, both because the personal equation enters in and because the conditions of life vary so much that there are no clearcut criteria that can be used.

For our classification we have used the following groups: 1. Patients who had made an improvement sufficient to allow them to resume their places in the life of the community and return to work we designated as "improved and working." This group is comparable to those described in the literature variously as having "complete remissions" and "full remissions." 2. Patients who had shown an improvement which allowed them to live outside a hospital, that is, who had become socially adjusted but who were not self-supporting, we classified as "improved but not working." This group might be considered as having "partial remission." 3. Patients who had shown physical and mental improvement, who were apparently maintaining a stationary condition so far as the disease was concerned and who were able to adjust well and work in the environment of a hospital for patients with mental disease we described as "improved but hospitalized." It may be pointed out that several of the patients in the second and third groups might well have been in the first group were it not for the economic depression. 4. Patients who had shown little or no improvement were considered as "unimproved." In the fifth group were placed patients who had died of any cause.

RESULTS

In table 2 we present an analysis of the clinical status of the entire group in 1934. The patients are divided according to the year in which treatment with malaria was given, according to the results obtained and, finally, according to the results in the entire group. The total indicates that, according to our analysis, 36.4 per cent of the 173 patients were improved and working in the year 1934 and 12.1 per cent were living outside of hospitals, although not self-supporting. Fifteen per cent, while remaining hospitalized, were thought to be definitely improved, all of them being able to do work in an institution and most of them having parole privileges; 13.8 per cent were living but unimproved, and 22.5 per cent had died.

According to this classification, 63.5 per cent of the patients had obtained good clinical improvement, and 48.5 per cent were living outside

TABLE 2.—*Clinical Status in 1934 of Patients with Dementia Paralytica Treated with Malaria from 1925 to 1931*

Year of Treatment	Number of Patients Treated	Clinical Condition, 1934				
		Improved: Working	Improved: Not Working	Improved: Hospitalized	Unimproved	Dead
Feb. 1925 to Feb. 1926	27	9	3	2	4	9
Feb. 1926 to Feb. 1927	27	9	2	4	5	7
Feb. 1927 to Feb. 1928	17	6	1	2	2	6
Feb. 1928 to Feb. 1929	28	9	5	5	3	6
Feb. 1929 to Feb. 1930	14	5	3	3	1	2
Feb. 1930 to Feb. 1931	60	25	7	10	9	9
Number treated from 1925 to 1931	173	63 (36.4%)	21 (12.1%)	26 (15%)	24 (13.8%)	39 (22.5%)

hospitals. These results are gratifying, but they show only a part of the total picture of therapeutic success, because the clinical results as recorded are limited to a large extent by the amount of damage to the brain that had occurred before therapy was begun.

In table 3 we present the observations on the cerebrospinal fluid. The observations for only 169 of the 173 patients are given because in the case of 4 it was not possible to make examinations of the spinal fluid subsequent to the treatment. We are not considering here the serologic reaction of the blood, because experience has definitely indicated that there is no relationship between the course of the disease and the reaction of the blood, either with or without adequate treatment. The spinal fluid, however, gives more satisfactory evidence of the effect of treatment on the disease process. While there is no complete parallelism between the clinical results and the observations on the spinal fluid, significant information is obtained from following the course of reaction of the spinal fluid. Wagner von Jauregg and his co-workers paid relatively little attention to the cerebrospinal fluid in their cases

because, as they pointed out, in many instances in which the response of the cerebrospinal fluid was good the patient did not show good clinical response, whereas, on the contrary, patients who showed marked improvement did not show a concomitant response in the cerebrospinal fluid. However, it is our opinion that a completely normal spinal fluid is a good indication of an arrest of the activity and progress of inflammation of the brain and represents an arrest of the disease. As has already been stated, even though the disease process is arrested, the clinical result may be poor because of the damage to the parenchymatous tissue which occurred previously. A summary of the observations on the spinal fluid in 1934 shows that completely normal fluid was obtained in 36.7 per cent of the patients and that an additional 20.7 per cent had markedly improved fluid. Another 18.3 per cent showed moderately

TABLE 3.—*Condition in 1934 of Cerebrospinal Fluid of Patients with Dementia Paralytica Treated with Malaria from 1925 to 1931*

Year of Treatment	Number of Patients Treated*	Cerebrospinal Fluid			
		Normal	Greatly Improved	Moderately Improved	Unimproved
Feb. 1925 to Feb. 1926	27	9	3	6	9
Feb. 1926 to Feb. 1927	25	16	3	2	4
Feb. 1927 to Feb. 1928	16	6	1	1	8
Feb. 1928 to Feb. 1929	28	10	7	5	6
Feb. 1929 to Feb. 1930	14	6	4	3	1
Feb. 1930 to Feb. 1931	59	15	17	14	13
Number treated from 1925 to 1931	169	62 (36.7%)	35 (20.7%)	31 (18.3%)	41 (24.3%)

* For 4 patients serologic data were not obtained; therefore a total of 169 patients are included in this table.

improved fluid, and in 24.3 per cent the fluid was considered as unimproved. By a "completely normal" fluid is meant a fluid showing a cell count under 5, a negative reaction for globulin, a total protein content under 40 mg. per hundred cubic centimeters, a negative reaction to the colloidal gold test and a negative Wassermann reaction with 1 cc. of fluid. A "greatly improved" fluid was one in which the reactions were very weak, approaching but not quite negative, whereas a "moderately improved" fluid showed a reasonable reduction from the original strongly positive formula.

With regard to the effect of treatment on the cerebrospinal fluid, as in the analysis of the clinical status, the figures presented give only a partial picture of the beneficial effects of treatment. It has been pointed out by other observers, notably by Ferraro and Fong,[2] that time plays an important rôle in the changes in the spinal fluid, e. g., within the first year after malarial treatment the number of cases in which one finds marked improvement in the fluid is much less than that found if the patients are examined again at the end of several

years. Thus, Ferraro and Fong stated: "The percentage of serological improvement increases grossly from a minimum of 15 per cent within the first six months, to a maximum of 86 per cent after a period of three years." It should be noted in comparing this statement with the results that we report that Ferraro and Fong referred to improvement and not to a normal fluid. Hinsie and Blalock [3] stated: "It appears that as the years go by negative laboratory luetic findings continue to increase." Likewise, White [4] showed that with time both the blood and the spinal fluid tend to show more and more negative reactions. Table 4 shows that the statements of the aforementioned authors are borne out by our own experience. As the years go by there are more and more patients with a normal cerebrospinal fluid. Thus, in 1 case the fluid did not become normal until eight years after the treatment with malaria, and in 5 cases seven years passed before this result was

TABLE 4.—*Time that Elapsed Before Cerebrospinal Fluid Became Normal*

Time Following Malarial Treatment	Number of Patients with Normal Fluid
Less than 1 year	1
1 year	2
1½ years	5
2 years	9
2½ years	9
3 years	6
3½ years	6
4 years	7
5 years	8
6 years	3
7 years	5
8 years	1
Total	62

obtained, whereas in only 3 cases did the fluid become completely normal in one year. In 32 of the 62 cases in which the fluid became normal the result was obtained in three years or less, whereas in the other 30 cases in which it became normal more than three years were required. It may also be pointed out that in 44 of the cases in which the spinal fluid did not become normal the period of observation subsequent to malarial treatment was less than four years. Further, we wish to emphasize that of the 41 patients whose fluid was unimproved, 24 died, and thus there may have been insufficient time for the fluid to become normal.

In our series we have dealt not only with the effect of a lapse of time following malarial treatment but also with the effect of subsequent treatment. Table 5 shows the amount of treatment that was given both prior to and subsequent to treatment with malaria in the cases in which a completely normal fluid was obtained. With regard to the effects

3. Hinsie, L. E., and Blalock, J. R.: The Treatment of General Paresis—Results of 197 Cases, 1923-1926, Am. J. Psychiat. **2**:541 (Nov.) 1931.

4. White, W. A.: Malarial Therapy of Paresis, Internat. Clin. **3**:298, 1931.

TABLE 5.—*Time that Elapsed After Malarial Treatment Before Cerebrospinal Fluid Became Normal; Treatment Received Before and After Malarial Therapy*

Patient	Time	Treatment Before Malarial Therapy, Doses	Treatment After Malarial Therapy, Doses
1. A. W.	10 mos.	None	42 tryparsamide
2. H. C.	12 mos.	None	33 tryparsamide
3. J. K.	14 mos.	Some arsphenamine	39 tryparsamide, 11 milk
4. H. L.	16 mos.	Virus of rat-bite fever, 18 typhoid vaccine	40 tryparsamide, 40 neoarsphenamine
5. B. E.	18 mos.	81 tryparsamide	19 tryparsamide, 20 bismuth
6. G. B.	18 mos.	None	75 tryparsamide
7. F. W.	18 mos.	90 tryparsamide, 30 mercury	60 tryparsamide, 20 bismuth
8. B. Mc.	20 mos.	None	None
9. W. H.	22 mos.	None	55 tryparsamide
10. C. H.	2 yrs.	None	50 tryparsamide, 4 bismuth
11. J. M.	2 yrs.	None	3 tryparsamide, 24 arsphenamine, 7 mercury
12. R. B.	2 yrs.	None	105 tryparsamide
13. T. Mc.	2 yrs.	None	5 tryparsamide, 7 arsphenamine, 3 mercury
14. W. L.	2 yrs.	173 tryparsamide	18 tryparsamide
15. B. L.	2 yrs.	None	110 tryparsamide
16. M. P.	2 yrs.	None	100 tryparsamide, 26 arsphenamine, 43 bismuth
17. L. P.	2 yrs.	None	23 tryparsamide
18. A. W.	2½ yrs.	Virus of rat-bite fever, 9 tryparsamide, 9 arsphenamine	50 tryparsamide
19. W. P.	2½ yrs.	Virus of rat-bite fever	52 tryparsamide
20. J. W.	2½ yrs.	15 typhoid vaccine	73 tryparsamide, 13 bismuth
21. M. M.	2½ yrs.	None	120 tryparsamide
22. A. L.	2½ yrs.	None	95 tryparsamide
23. B. B.	2½ yrs.	None	40 tryparsamide
24. D. Mac.	2½ yrs.	None	100 tryparsamide
25. J. B.	2½ yrs.	None	5 tryparsamide, 18 sulpharsphenamine, 74 bismuth, 19 diathermy
26. H. T.	2½ yrs.	None	130 tryparsamide
27. C. B.	3 yrs.	None	140 tryparsamide
28. R. D.	3 yrs.	50 tryparsamide	75 tryparsamide
29. A. V.	3 yrs.	69 tryparsamide	90 tryparsamide, 10 bismuth
30. T. O.	3 yrs.	None	5 arsphenamine, 6 sulpharsphenamine, 19 bismuth, 30 mercury
31. J. D.	3 yrs.	None	75 tryparsamide
32. J. T.	3 yrs.	None	5 tryparsamide, 8 typhoid vaccine, 21 mercury, 47 arsphenamine
33. J. Mc.	3½ yrs.	None	40 tryparsamide
34. L. G.	3½ yrs.	None	150 tryparsamide
35. L. K.	3½ yrs.	None	77 tryparsamide, 21 neoarsphenamine
36. C. D.	3½ yrs.	None	64 tryparsamide, 24 neoarsphenamine
37. J. B.	3½ yrs.	None	20 tryparsamide, 13 arsphenamine, 44 bismuth

TABLE 5.—*Time that Elapsed After Malarial Treatment Before Cerebrospinal Fluid Became Normal; Treatment Received Before and After Malarial Therapy—Continued*

Patient	Time	Treatment Before Malarial Therapy, Doses	Treatment After Malarial Therapy, Doses
38. K. B.	3½ yrs.	95 tryparsamide, 26 mercury, 41 arsphenamine	90 tryparsamide
39. J. B.	4 yrs.	15 typhoid vaccine	31 arsphenamine, 28 bismuth, 23 mercury
40. P. Mc.	4 yrs.	None	3 tryparsamide
41. R. M.	4 yrs.	None	100 tryparsamide
42. L. G.	4 yrs.	None	100 tryparsamide
43. J. M.	4 yrs.	None	72 tryparsamide, 10 milk
44. J. Mc.	4 yrs.	None	120 tryparsamide
45. J. C.	4 yrs.	None	13 typhoid vaccine, 25 neoarsphenamine, 12 arsphenamine, 12 bismuth, 12 mercury
46. J. V.	5 yrs.	None	200 tryparsamide
47. J. M.	5 yrs.	Virus of rat-bite fever	51 tryparsamide
48. J. O.	5 yrs.	None	65 tryparsamide
49. F. T.	5 yrs.	None	150 tryparsamide, 30 neoarsphenamine
50. G. A.	5 yrs.	None	70 tryparsamide, 30 bismuth
51. B. A.	5 yrs.	72 tryparsamide	8 tryparsamide, 15 typhoid vaccine
52. F. Mc.	5 yrs.	None	132 tryparsamide, 20 neoarsphenamine, 80 bismuth
53. F. B.	5 yrs.	None	8 tryparsamide, 5 neoarsphenamine, 10 sulpharsphenamine
54. H. S.	6 yrs.	None	9 tryparsamide
55. J. B.	6 yrs.	None	27 tryparsamide, 54 arsphenamine, 57 bismuth, 12 mercury, virus of rat-bite fever, erysipelas
56. T. Mc.	6 yrs.	None	180 tryparsamide, 30 mercury
57. M. W.	7 yrs.	None	22 tryparsamide, 41 arsphenamine, 12 bismuth, 55 mercury, virus of rat-bite fever
58. J. Y.	7 yrs.	None	27 arsphenamine, 70 mercury
59. P. B.	7 yrs.	None	153 tryparsamide
60. F. A.	7 yrs.	23 tryparsamide	28 tryparsamide, 25 arsphenamine, 27 sulpharsphenamine
61. J. L.	7 yrs.	59 arsphenamine, 75 tryparsamide, 22 injections given according to the Swift-Ellis method	20 tryparsamide, 39 bismuth
62. R. H.	8 yrs.	None	41 tryparsamide, 16 bismuth

of time and treatment on the spinal fluid, it is significant that in only 1 case was there a strongly positive reaction of the fluid after five years, and in only 3 cases was the fluid merely greatly improved after five or more years of treatment.

We have already referred to the statements in the literature that there is little parallelism between the clinical and the serologic results. In table 6 is given an analysis of the relationship between the clinical and the serologic results in our series. From this analysis one can find little definite correlation between the clinical status and the serologic reactions. This is due largely to the fact that the great majority of patients who live for any length of time after the treatment show considerable improvement serologically. Here again we wish to emphasize that clinical results, so-called, deal with the mental capacity of the patient rather than with the question of the arrest of the disease, and so we find that of 24 patients considered unimproved clinically, 12 had

TABLE 6.—*Relationship Between Clinical and Serologic Results in 1934*

Clinical Results	Number of Patients	Condition of Spinal Fluid				
		Normal	Greatly Improved	Moderately Improved	Unimproved	No Tests
Improved: working	63	25	18	13	6	1
Improved: not working	21	5	5	6	4	1
Improved: hospitalized	26	16	6	3	1	..
Unimproved	24	12	5	2	6	..
Dead	39	4	1	7	24	2
Totals	173	62	35	31	41	4

a normal spinal fluid. These were patients in whom the disease had apparently been arrested but the functional capacity continued to be low. It seems to us that this group of patients demonstrates most clearly the beneficial effects of treatment. They were patients in whose cases no one could question the correctness of the diagnosis of dementia paralytica and who showed excellent evidence of a complete arrest of the disease process as the result of treatment.

We have already mentioned that we made some selection of patients to be treated; hence a few words concerning the matter of selection may not be out of order. We have been particularly struck over a period of years by the impracticability of making a good prognosis before treatment. On a number of occasions we have treated a patient who seemed to us to present a particularly poor risk because of his clinical condition and have obtained an excellent therapeutic effect. On the other hand, in several instances a patient who was selected because he was young, in good physical condition and vigorous and had had evidence of psychosis for a very short period has shown results that were entirely unsatisfactory. Our conclusion on this point is that

the criteria for judging "good" and "bad" cases before treatment are usually unsatisfactory. Of course, in cases in which the psychosis has gone on for a relatively long period with marked deterioration or in which the physical condition is extremely poor, one may feel almost certain that treatment will be of no avail. For example, Warner [5] reported that in 70 of his series of 131 cases the treatment was started within two years of the onset of the psychosis; he recorded remission in 60 per cent of these cases, whereas of 61 patients who were treated in the later stages of a psychosis only 18 per cent were reported to be definitely improved. Once more we wish to call attention to the fact

TABLE 7.—*Clinical Results by Age Groups*

Age Groups, Years	Number of Patients	Condition				
		Improved: Working	Improved: Not Working	Improved: Hospitalized	Unimproved	Dead
20 to 29	10	5	1	1	1	2
30 to 39	60	23	9	13	5	10
40 to 49	69	25	7	7	12	18
50 to 59	31	9	4	5	5	8
60 to 69	3	1	0	0	1	1
Total	173	63	21	26	24	39

TABLE 8.—*Serologic Results by Age Groups*

Age Groups, Years	Number of Patients	Condition of Spinal Fluid			
		Normal	Greatly Improved	Moderately Improved	Unimproved
20 to 29	10	4	3	1	2
30 to 39	57	22	11	13	11
40 to 49	68	27	12	10	19
50 to 59	31	9	7	7	8
60 to 69	3	0	2	0	1
Total	169	62	35	31	41

that these results deal with the functional capacity of the patient rather than with a question of the arrest of the pathologic process.

The question of age as a basis for treatment or refusal of treatment frequently arises. In tables 7 and 8 we give the clinical and serologic results according to age groups. From this material it appears that age is an unimportant factor. Certainly the patients in the age group from 60 to 69 appear to have done as well from both standpoints as those in the age group from 20 to 29.

We shall now consider the clinical results obtained in the series of patients under treatment in comparison with the results when no treatment is administered. A tendency to improve or to go into what is

5. Warner, George: A Second Report on Malarial Therapy in General Paresis, Psychiatric Quart. **3**:605, 1929.

called spontaneous remission is one of the characteristics of dementia paralytica, and there are many analyses of spontaneous remission in the period before the type of treatment now under discussion was administered, when treatment was limited or was entirely ineffectual. The recorded incidence of such spontaneous remission varies from 2 to 3 per cent, as found by some observers, to as much as 20 per cent, as noted by others. Loman,[6] in a survey of cases of patients untreated at the Boston State Hospital, found that there was spontaneous remission in 8 per cent. At any rate, spontaneous remissions rarely last a year, and in retrospect one can see that in a good percentage of the patients who had a long-maintained natural remission the remission occurred as the result of intercurrent febrile diseases which had an unrecognized therapeutic effect. It should also be pointed out that in the spontaneous remission, in most instances at any rate, there is no change in the observations on the cerebrospinal fluid, the results differing in this respect from those of a remission which is produced therapeutically.

The life expectancy of untreated and treated patients with dementia paralytica is an interesting and significant subject for comparative study. The expectancy for untreated patients is not great. According to Mott:[7] "The average time is about two years in man and three years in woman . . . Rather more than half died within one year of admission to the asylum." Hinsie and Blalock[3] stated: "It may be presumed that the average patient with general paresis who dies while in the hospital spends about one and a half years in the hospital." In marked contrast is the period of survival of the patients in our series (table 9), 134 of the 173 patients, or 77.5 per cent, having lived three or more years. If one considers the patients treated up to 1929, allowing a period of from five to nine years from the time of treatment to that of the analysis, it is found that 71.7 per cent were living.

An analysis of the cases of patients who died is given in table 10. Four of the deaths may be definitely attributed to malaria, giving a mortality due to the treatment of 2.3 per cent. It is possible that several other patients may have been so weakened by the malarial treatment that death from other causes was facilitated. However, it appears that under careful management the mortality caused by the treatment is not great. We have attributed 25 of the 39 deaths to dementia paralytica. In other words, we have considered that in 25 of the 39 cases that ended in death, in addition to the 4 in which the patient died as the result of malaria, we were unable to arrest the progress of the disease. As time goes

6. Loman, Julius: Comparison of Treated and Untreated Cases of General Paresis, Bull. Massachusetts Dept. Ment. Dis. **15**:18 (April) 1931.

7. Mott, F. W.: Syphilis of the Nervous System, in Power, D'Arey, and Murphy, J. K.: A System of Syphilis, ed. 2, New York, Oxford University Press, 1914, vol. 4, p. 287.

on it may be found that more cases properly belong in the group in which therapy was not potent in preventing death from the disease, the mortality from which when treatment is not given approaches 100 per cent. At any rate, it seems obvious that life can be greatly prolonged in a high percentage of cases.

TABLE 9.—*Period of Survival of Patients Treated with Malaria*

Year of Treatment	Number of Patients Treated	Number Living, 1934	Number Dead
Feb. 1925 to Feb. 1926	27	18	9
Feb. 1926 to Feb. 1927	27	20	7
Feb. 1927 to Feb. 1928	17	11	6
Feb. 1928 to Feb. 1929	28	22	6
Feb. 1929 to Feb. 1930	14	12	2
Feb. 1930 to Feb. 1931	60	51	9
Total to 1931	173	134*	39

* Of the entire series 77.5 per cent were living in 1934, having a period of survival of three or more years.

TABLE 10.—*Analysis of Thirty-Nine Fatal Cases and Causes of Death According to Years that Elapsed Following Malarial Treatment*

Deaths Following Treatment	Number of Deaths	Causes of Death			Comment
		Malaria	Dementia Paralytica	Other Causes	
First year	18	4	11	Suicide: 1*	Showed mental improvement before death
				Chronic valvular heart disease: 1*	Showed mental improvement before death
				Cardiac decompensation: 1	
Second year	8	0	6	Chronic nephritis: 1*	Showed mental improvement before death
				Acute peritonitis: 1	Autopsy revealed gangrene of the rectum
Third year through the eighth year	13	0	8	Bronchopneumonia: 1*	Clinical remission one year before death
				Gangrene of the lung: 1	Autopsy revealed syphilitic aortitis and coronary thrombosis
				Pneumococcic meningitis: 1	Autopsy revealed acute leptomeningitis (pneumococcic type) and acute myocarditis
				Lobar pneumonia: 1	Autopsy revealed little to suggest dementia paralytica
				Suicide: 1*	Showed mental improvement before death

* This patient was considered to be clinically improved; the cause of death is indicated.

In our series there were only 9 women among the 173 patients considered, so we feel that we have nothing to contribute on the question of the difference in the effects of treatment on male and on female patients. As a matter of completeness of the data, we give the following summary of the status of the female patients: One patient was improved and working; 2 were improved but were not working; 3 were

improved but were hospitalized; 2 were unimproved, and 1 had died. The serologic tests showed that in 2 the spinal fluid was completely normal; in 1 the fluid was greatly improved; in 4 there was moderate improvement, and in 2 there was no improvement.

In the literature on the subject, a number of analyses have been made of the effect of treatment on patients showing different clinical syndromes of the psychoses, that is, patients with simple demented, expansive, manic, depressed, paranoid and agitated forms of dementia paralytica. We realize that our series is not large enough to permit an analysis of this sort, and we do not believe that any of the analyses we have seen are of great significance. In general, however, it may be said that patients presenting a paranoid syndrome with a picture suggestive of a schizophrenic psychosis rarely make a good clinical adjustment; even when the disease process is arrested they show a disorganization of personality. It is of interest to note that after malarial therapy there is occasionally considerable change in the clinical picture of the psychosis in patients who do not present improvement. In a few cases the patient passes into a clinical state that is suggestive of a schizophrenic pattern, with paranoid delusions, seclusiveness and hallucinatory experiences. Of our group of 173 patients, none showed typical hallucinatory phenomena prior to treatment with malaria, whereas subsequently 13, or approximately 7.5 per cent, had definite hallucinations in the auditory sphere.

It has already been mentioned that some of the patients received treatment prior to inoculation with malaria. The question arises as to whether prior treatment, particularly with arsenicals, is of advantage or of disadvantage. It is not possible from our experience to draw a well substantiated conclusion. From table 5 it will be seen that in the cases in which completely negative serologic results were obtained, 11 of 62 patients had received arsenicals in considerable amounts prior to the treatment with malaria, whereas 51 had not. We have not been able to convince ourselves that a great difference in the result is to be obtained with or without antecedent treatment with arsenicals. However, we have had experience enough to convince us that patients who are not progressing well on arsenical therapy alone may show marked improvement following treatment with malaria.

SUMMARY

On analyzing in February 1934 the results obtained in a group of 173 patients suffering from dementia paralytica who were treated by inoculation with malaria between February 1925 and February 1931 and who received other treatment as well, we found that good improvement from the clinical standpoint was obtained in 36.4 per cent and that definite improvement was obtained in an additional 27.1 per cent.

The serologic results in 169 of the patients who could be followed subsequently indicated a completely normal spinal fluid in 36.7 per cent, a greatly improved spinal fluid in 20.7 per cent and a somewhat improved fluid in 18.3 per cent.

As a result of our analysis we are ready to state that the process of dementia paralytica can be arrested in a great majority of cases if treatment is instituted before the disease has progressed too far and if the general physical condition of the patient, aside from the involvement of the central nervous system, is sufficiently good to allow him to take this rather radical treatment and allow for a reasonable length of life. This statement is based on the fact that normal or nearly normal reactions of the spinal fluid are obtainable in the course of years in such a large percentage of cases that the life expectancy is increased by years and that the progress of the mental disease is arrested.

If one considers only the final clinical state of the patient there will be many disappointments. This, we believe, is because the irreparable ravages of the spirochetal infection have already gone far in many cases before treatment is instituted.

The best method of treating patients with dementia paralytica cannot be determined, in our opinion, at the present time. In our series various other types of treatment were given in addition to the malarial therapy in a large percentage of the cases. Such treatment consisted of injections of drugs, particularly of tryparsamide and of arsphenamine, the administration of bismuth, mercury and the iodides and fever induced by the virus of rat-bite fever, by injection of typhoid vaccine milk and by diathermy. It is our impression that a combination of other methods with malarial therapy gives more satisfactory results than treatment with malaria alone.

RESPIRATORY METABOLISM OF EXCISED BRAIN TISSUE

II. THE EFFECTS OF SOME DRUGS ON BRAIN OXIDATIONS

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Much work is being done on the respiratory metabolism of central and peripheral nerve tissue. Ashford,[1] Dickens and Greville,[2] Holmes,[3] Himwich and his co-workers,[4] Peters and Sinclair,[5] Quastel and Wheatley,[6] Wortis [7] and others have recently reported such studies. It has been the aim of most workers in this field (1) to determine the nature of the foodstuffs utilized by various animal tissues and (2) to measure, when possible, the ability or limitation of ability of nerve tissue to continue such normal oxidation of foodstuffs under the influence of disease or drugs.

METHODS

Experimental approach to these problems has been accomplished mainly by two technical methods: The first one is the Barcroft-Warburg method,[8] wherein small amounts of accurately weighed living tissue are kept under nearly physiologic conditions and the gaseous metabolism (i. e., the oxygen consumption and carbon dioxide production) is accurately measured. Recently, the manometric modification of Dickens and Greville [2] has been perfected.

The second method consists of simultaneous arterial and venous puncture, with an analysis of the blood entering and leaving the organ. The oxygen content and the carbon dioxide content of the blood are determined by the method of gas analysis described by Van Slyke and Neill. For studies of the metabolism of the brain, samples are taken from the internal carotid artery and the deep internal jugular vein.

By either method one may measure the respiratory quotient, which gives information concerning the nature of the foodstuffs being oxidized. From the known

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1. Ashford, C. A.: Biochem. J. **27**:903, 1933.

2. Dickens, F., and Greville, A.: Biochem. J. **27**:832, 1932.

3. Holmes, E.: Biochem. J. **25**:1119, 1930.

4. Himwich, H.; Fazikas, J. F.; Rakieten, N., and Sanders, R.: Proc. Soc. Exper. Biol. & Med. **30**:903, 1933.

5. Peters, R. A., and Sinclair, H. M.: Biochem. J. **27**:1677, 1933.

6. Quastel, J. H., and Wheatley, A. H. M.: Biochem. J. **27**:1609, 1933.

7. Wortis, S. Bernard: Am. J. Psychiat. **13**:725 (Jan.) 1934.

8. Warburg, O.: The Metabolism of Tumors, translated by Frank Dickens. New York, Richard R. Smith, Inc., 1931.

chemical composition of the basic foodstuffs, one can calculate the characteristic respiratory quotient for carbohydrate or lactic acid to be 1, that for protein to be 0.82 and that for fat, 0.7. In addition, the oxygen consumption per unit of tissue weight per unit of time can also be measured. Furthermore, by placing normal minced brain tissue in physiologic solutions containing various foodstuffs and measuring by exact chemical quantitative methods the concentration of such foodstuffs in the solution at the beginning and at the end of an accurately timed experiment, one can determine the ability and rate with which a normal brain utilizes such food. In addition, by analyzing (for sugar and lactic acid) samples of blood entering and leaving the brain, one can determine the ability of this organ to take from or add to the blood foodstuffs like sugar or lactic acid.

Each of the methods enumerated has its particular technical advantages and its definite limitations. The work reported in this communication was done by the Barcroft-Warburg manometric technic. For most of the experiments white male rats weighing 250 Gm. were used. Brain tissue in most instances was obtained by rapidly decapitating the animals without previous anesthesia. Chemical determinations for lactic acid were made by the method of Friedemann, Cotonio and Shaffer,[9] and for sugar by the method of Hagedorn and Jensen.[10] All experiments were carried out in Ringer's phosphate solution,[10a] as used by Warburg, buffered to p_H 7.4 at 37.5 C.

RESULTS

Respiratory Quotient of Brain Cortex and Spinal Cord.—The details of the technic have been described in previous studies.[8] The results indicate that the brain of normal warm-blooded animals so far studied (man and the monkey, cat, dog, rat and mouse) yields a respiratory quotient of 1, indicating that brain tissue normally oxidizes carbohydrate or lactic acid. Food starvation (studied in the cat) for two weeks does not affect the respiratory quotient of the excised brain tissue.

Minced normal spinal cord tissue (monkey and cat) also yields a respiratory quotient of 1. Other animal tissues have their specific normal oxidative metabolism. For example, in the white rat the respiratory quotient of kidney tissue is 0.85 and of liver tissue, 0.77, and in the cat the respiratory quotient of tissue from the meninges is 0.86.

Effects of Dextrose and Sodium Lactate.—The addition of dextrose or sodium lactate to the fluid used for immersion stimulates respiration in surviving excised brain and spinal cord tissue. Conversely, the respiration rate of adult brain tissue decreases rapidly when it is deprived

9. Friedemann, T.; Cotonio, M., and Shaffer, P. A.: J. Biol. Chem. **73**:335 (May) 1927.

10. Hagedorn and Jensen: Biochem. Ztschr. **135**:46, 1923; **137**:92, 1923.

10a. Ringer's solution is made as follows: 1,000 cc. of physiologic solution of sodium chloride (9 Gm. of sodium chloride per liter of water), 20 cc. of potassium chloride solution (11.5 Gm. of potassium chloride per liter of water) and 20 cc. of calcium chloride solution (12.2 Gm. of calcium chloride per liter of water). Phosphate solution to buffer saline or Ringer's solutions is made with 2 cc. of M/15 sodium di-hydrogen phosphate solution mixed with 8 cc. of M/15 di-sodium hydrogen phosphate solution. By diluting this mixture to 1:10 with 0.9 per cent saline solution, a M/150 solution with p_H 7.4 is obtained.

of dextrose. This oxidative stimulation seems to vary directly with the concentration (within physiologic limits) of such foodstuffs in the substrate (chart 1). Holmes [3] and Dickens and Greville [2] demonstrated this effect. Fructose is also oxidized by both brain and retina with a respiratory quotient of 1, "probably without intermediate conversion into lactic acid." [2] Dickens and Greville showed further that "the respiration of embryonic tissues falls very little when they are deprived of glucose. They appear to contain reserve foodstuffs of whose nature we are ignorant." Quastel and Wheatley [6] studied the oxidation by the brain tissue of the succinic acid series and showed that lactate, pyruvate and glycerophosphate are all "oxidized." Peters and Sinclair confirmed this work on normal pigeon brain.

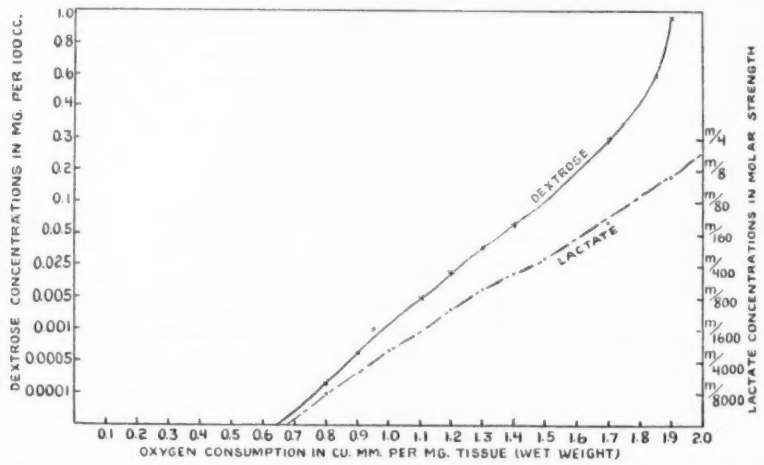

Chart 1.—The effect of different concentrations of dextrose and sodium lactate in Ringer's phosphate solution (buffered to p_H 7.4 at 37.5 C.) on the oxygen consumption of excised brain tissue over a period of two hours.

Ashford [1] recently published studies on the glycolytic mechanisms of the brain and showed that the breakdown of dextrose to lactic acid by brain tissue is not inhibited by the presence of glycogen. He offered evidence to show that brain tissue contains two mechanisms for the production of lactic acid.

Effects of Some Drugs.—The ability of sedatives to diminish oxidation by brain tissue has only recently been studied by manometric methods. It is important to emphasize that all sedatives do not appear to interfere equally with the access of oxygen to, or its activation by, brain cells (chart 2). Quastel and his co-workers [11] demonstrated that

11. Quastel, J. H., and Ström-Olsen, R.: Lancet **1**:464 (March 4) 1933. Quastel and Wheatley.[6]

"narcotics, in general, inhibit the oxidation by brain of glucose, sodium lactate and sodium pyruvate, but do not inhibit the oxidation of sodium succinate and p-phenylenediamine." They also showed that of "narcotics belonging to the same chemical type, those with the greater hypnotic activity have the greater inhibitive action on brain oxidations."

To study these problems further I have used two methods to measure the effects of sedatives and other drugs on oxidation by brain tissue.

1. Injection of different drugs into normal white rats was carried out until narcosis (for sedatives) or convulsions (for insulin) resulted (table 1). The animal's brain was then removed by cutting across the

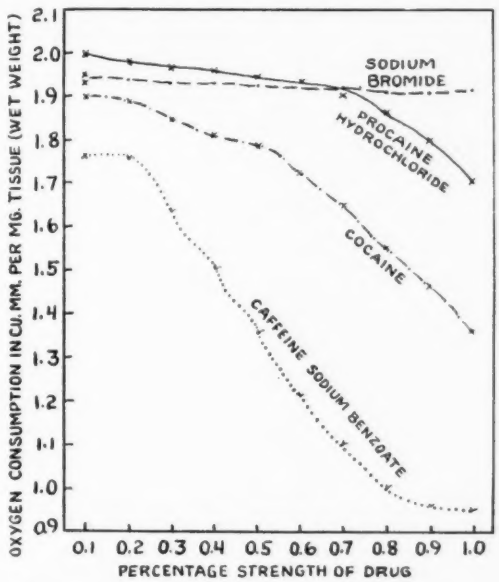

Chart 2.—The effect of some drugs in 0.2 per cent dextrose with Ringer's phosphate solution (buffered to p_H 7.4 at 37.5 C.) on the oxygen consumption of excised brain tissue over a period of two hours.

neck, and the respiratory metabolism of the brain tissue was studied over a period of two hours in the Barcroft-Warburg unit. Table 1 shows the results obtained. Morphine, butyl-bromallyl barbituric acid and sodium amytal do not appear to affect the respiratory quotient or the oxygen consumption over a period of two hours, when the results are compared with those obtained with normal brain tissue. Study of the brain tissue after insulin was injected (to the point of causing convulsions in previously starved animals) showed a marked depression of the respiratory quotient to 0.75 (in a plain buffered Ringer phosphate solution), with a corresponding depression of the oxygen

consumption. Ethyl alcohol also depressed the respiratory quotient to 0.93, indicating (as Himwich previously noted) the ability of brain tissue to oxidize small quantities of alcohol.

2. Normal brain tissue was immersed in fluids containing various drugs at different concentrations, and the respiratory quotient and the

TABLE 1.—*Respiratory Quotient and Oxygen Consumption in Cubic Millimeters Per Milligram of Wet Weight of Minced Brain Tissue from Animals Given Injections of Different Drugs*

		Respiratory Quotient		Oxygen Consumption			
				Ringer's Phosphate Solution, Plain		Ringer's Phosphate Solution with 0.2% Dextrose	
Drug	Animal	Ringer's Phosphate Solution, Plain	Ringer's Phosphate Solution with 0.2% Dextrose	60 Min.	120 Min.	60 Min.	120 Min.
Sodium amytal intraperitoneally	Rat	1.00	0.95	0.81	1.40	1.03	1.98
Sodium amytal intramuscularly	Rat	0.99	0.93	0.78	1.35	1.17	2.23
Sodium amytal intravenously (to narcosis)	Cat	0.96	1.00	0.81	1.19	0.79	1.53
Morphine, ½ grain (0.32 Gm.)	Rat	1.01	1.07	0.93	....	1.07	....
Butyl-bromallyl barbituric acid, 1 cc.	Rat	1.01	0.96	0.85	1.50	1.08	2.10
Ethyl alcohol, 50 cc. of 19% solution per Kg. of body weight (to deep narcosis)	Rat	0.93	0.93	0.85	1.47	1.14	2.18
Ethyl alcohol, 50 cc. of 19% solution per Kg. of body weight (to deep narcosis)	Rat	0.94	0.96	0.65	1.06	1.21	2.20
Ethyl alcohol, 50 cc. of 50% solution intravenously	Cat 10 lbs.	0.98	0.97	0.87	1.56	0.85	1.60
Insulin, 3 day period of food starvation; insulin injected until convulsions occurred	Rat	0.75	0.95	0.42	0.70	1.14	2.23
Insulin, 2 day period of food starvation; insulin injected until convulsions occurred	Rat	0.73	0.92	0.28	0.51	1.03	1.89
Illuminating gas, inhalation until deep coma developed	Rat	0.94	0.95	0.67	1.19	1.02	2.02
Illuminating gas, inhalation until deep coma developed	Rat	0.96	0.97	0.69	1.20	1.15	2.35
No drug	Normal rat 240 Gm.	1.00	1.01	0.72	1.14	1.09	2.12
No drug	Rat	1.00	1.02	0.86	1.44	1.30	2.59
No drug	Normal cat	1.05	1.00	0.66	1.23	0.84	1.65

oxygen consumption were subsequently measured over a period of two hours. Table 2 shows that cocaine, sodium cyanide and methylthionine chloride, U. S. P. (methylene blue), in the concentrations used, appeared to depress the respiratory quotient and the oxygen uptake. Phenobarbital sodium (0.5 per cent solution), although it did not affect the respiratory quotient, depressed the oxygen consumption of brain tissue. Sodium bromide, although it did not affect the respiratory quotient, appeared to depress the ability of brain tissue to oxidize foodstuffs as rapidly as under normal conditions.

Minced normal brain tissue of the rat was immersed in a buffered Ringer phosphate solution and the lactic acid content measured by chemical quantitative methods at the beginning and at the end of two

TABLE 2.—*Respiratory Quotient and Oxygen Consumption in Cubic Millimeters Per Milligram of Wet Weight of Minced Normal Brain Tissue Immersed in Solutions of Different Drugs*

		Respiratory Quotient		Oxygen Consumption			
				Ringer's Phosphate Solution, Plain		Ringer's Phosphate Solution with 0.2% Dextrose	
Drug	Animal	Ringer's Phosphate Solution, Plain	Ringer's Phosphate Solution with 0.2% Dextrose	60 Min.	120 Min.	60 Min.	120 Min.
Procaine hydrochloride							
0.5%	Rat	1.02	1.04	0.68	1.19	1.06	1.99
Morphine sulphate							
0.032%	Rat	1.05	0.94	0.68	1.15	1.20	2.32
0.008%	Rat	0.99	0.99	0.79	1.33	1.08	2.17
Phenobarbital sodium							
0.5%	Rat	1.03	1.03	0.23	0.40	0.53	0.89
Insulin							
1 unit per cc. of immersion fluid	Rat	0.99	1.00	0.82	1.38	1.19	2.37
Cocaine hydrochloride							
0.5%	Rat	0.79	0.95	0.43	0.60	1.08	1.92
Caffeine sodiobenzoate							
0.5%	Rat	0.96	1.00	0.53	0.88	0.98	1.72
Sodium bromide							
0.1%	Rat	....	0.97	....	....	0.75	1.53
0.05%	Rat	0.99	1.00	0.63	1.12	0.92	1.95
1.0%	Rat	0.93	0.99	0.56	0.94	1.01	1.99
			M/800 sodium lactate			M/800 sodium lactate	
Sodium cyanide							
0.006%	Rat	0.94	0.74	0.20	0.37	0.28	0.48
			0.2% dextrose			0.2% dextrose	
Ergotine phosphate							
0.01%	Rat	1.07	1.02	0.70	1.19	1.06	2.04
Sodium fluoride							
0.002%	Rat	....	0.95	....	....	0.99	1.96
0.005%	Rat	....	0.91	....	....	1.00	1.87
0.01%	Rat	....	0.94	....	....	1.00	1.93
Strychnine sulphate							
0.009%	Rat	0.94	0.95	0.68	1.19	0.95	1.91
Methylthionine chloride							
0.006%	Rat	0.70	0.80	0.31	0.42	0.64	0.81
			M/800 sodium lactate			M/800 sodium lactate	
0.005%	Rat	0.94	0.63	0.34	0.49	0.32	0.44
			0.2% dextrose			0.2% dextrose	
Hyoscine hydrobromide							
0.009%	Rat	0.98	0.95	0.66	1.16	0.95	1.82
0.007%	Rat	0.98	0.98	0.86	1.43	1.18	2.30
Nicotine							
0.008%	Rat	1.03	1.01	0.77	1.37	1.10	2.27
0.02%	Rat	1.03	0.98	0.77	1.26	1.23	2.41
Intravenous injection, then brain was removed; 25 mg. of nicotine	Cat, 5 lbs.	0.98	1.03	0.79	1.45	0.92	1.78

hours. It will be seen from the protocol presented in table 3 that the presence of sodium bromide diminished the oxidative metabloism quantitatively but not qualitatively (i. e., the respiratory quotient remained 1 as in normal brain tissue but less food was oxidized in the presence of sodium bromide).

Holmes [3] showed that the lactic acid content of brain tissue after convulsions induced by the injection of insulin is lower than that of normal brain tissue measured by the same methods and at equal intervals of time after decapitation. I have confirmed his findings.

Rat Brain	Lactic Acid, Mg. per 100 Gm. (average)
Normal	75
After insulin had been injected to produce convulsions	45

Johansson [12] showed that in a concentration of four-tenths molar and at p_H 7.4, ethyl carbonate (urethane) greatly inhibits the rate of oxidation of brain tissue of the rabbit.

Quastel and Wheatley [6] investigated further the effects of some amines on oxidation by brain tissue and showed that β-phenylethylamine,

TABLE 3.—*Effect of Sodium Bromide on Food Oxidation by Brain*

	Ringer's Phosphate Solution with 0.2% Dextrose	Ringer's Phosphate Solution with 0.2% Dextrose Plus 0.5% Sodium Bromide	Ringer's Phosphate Solution, Plain	Ringer's Phosphate Solution, Plain, Plus 0.5% Sodium Bromide
Initial lactic acid content, mg. per 100 Gm.	118.0	80.5	87.5	49.0
Final lactic acid content, mg. per 100 Gm. (after 2 hour experiment)	71.0	60.5	66.0	43.5
Difference: mg. of lactic acid per 100 Gm.	47.0	20.0	21.5	5.5

β-phenyl-β-hydroxyethylamine, tyramine, indole, iso-alamine, and mescaline strongly inhibit the oxidation of dextrose, sodium lactate and sodium pyruvate by the brain tissue. They emphasized the similarity of the action of these drugs to the depressing effect of narcotics on oxidation by the brain.

Each of the figures reported in the tables is the average of from four to six experiments. Caffeine sodium benzoate in high concentration diminishes the oxygen consumption of normal brain tissue. This effect may be partly an artefact and due to tissue damage. However, when normal brain tissue of the rat is immersed in a solution of 0.5 per cent caffeine sodium benzoate in 0.2 per cent dextrose the respiratory quotient remains normal. The dextrose in the immersion medium evidently can act as a protector of the normal oxidizing function of the tissue.

CONCLUSIONS

The biochemical approach to the problem of cellular physiology of nerve tissue in normal and pathologic states is beginning to yield important data. Normal brain and spinal cord tissue has a respiratory

12. Johansson, H.: Skandinav. Arch. f. Physiol. **63**:90, 1931.

quotient of 1. Peters has recently shown in polyneuritic pigeons with a deficiency of vitamin B_1 that the ability of their brain tissue to oxidize lactic acid is diminished. Himwich and his co-workers [4] confirmed this work by showing that the respiratory quotient of brain tissue in animals suffering with B_1 avitaminosis was 0.89 instead of 1 for normal animals.

I shall not attempt here a discussion of the theories of narcosis; recent reviews of Henderson [13] and Winterstein cover this problem in great detail. Suffice it to note that all sedatives apparently do not act by simply depressing all the oxidative mechanism of brain tissue. As Quastel and Wheatley [6] suggested (and as von Economo [14] postulated on evidence adduced by decerebrating animals and then noting the effects of sedatives), there is good reason to believe that the specificity of different hypnotics is due to their being specifically absorbed and acting on different parts of the brain. Narcotics do not prevent the access of oxygen to brain tissue.

Insulin diminishes the oxygen consumption by brain tissue, and this cellular anoxemic effect may possibly account for the clinical symptomatology (confusion, excitement and convulsions) that one sees in cases of hyperinsulinism due to hypersecretion by adenomas of the islands of Langerhans.

Study of the metabolism of brain and spinal cord tissue in specific disease entities may help one to understand and possibly to correct some discoverable aberrations in the physiology of nerve tissue.

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13. Henderson, V. E.: Physiol. Rev. **10**:171, 1930.
14. von Economo, C.: Rev. neurol. **34**:837, 1927.

CAFFEINE SODIOBENZOATE, SODIUM ISO-AMYLETHYL BARBITURATE, SODIUM BROMIDE AND CHLORAL HYDRATE

EFFECT ON THE HIGHEST INTEGRATIVE FUNCTIONS

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The purpose of this communication is to present a description of the effects of caffeine sodiobenzoate, sodium iso-amylethyl barbiturate, sodium bromide and chloral hydrate on the highest integrative functions. The acquired or conditioned response has been taken as an expression of these functions. For experimental purposes standard methods of testing have been adopted and a measurable component of the conditioned response quantitatively studied. The effects of the aforementioned agents have been compared with other factors that alter responses involving the highest integrative functions.

Animals with a relatively well developed cerebral cortex are characterized as a group by their ability to effect temporary connections between their constantly changing external environment and various activities of their physiologic households. In the broadest terms, it may be said of the group that if there is a coincidence in time of any external stimulus with some activity of the organism, this activity may subsequently be evoked by that external stimulus.

In other words, such animals have the ability to react in a special way to a variety of stimuli, in themselves biologically inconsequential, when these stimuli have been previously coupled directly or indirectly with the occurrence of some biologically significant experience. Such experiences include any act remotely or immediately involved in processes like feeding, reproduction and self-preservation. Moreover, these temporary and unitary reactions are elicited by and dependent on the stimulus, and they depend to a greater extent and far more than any other type of reaction on the conditions existing at the time the stimulus is presented. Thus, a stimulus which under one set of circumstances elicits one reaction may under other conditions evoke the opposite response.

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Should the coincidence of the inconsequential stimulus and significant biologic activity occur often enough and the conditions of the association remain otherwise constant, the reaction may become so regular and predictable as to justify its use as a means of measuring the most complex function for the adjustment of the organism to its environment.

By virtue of this ability the animal develops and readily utilizes new, acquired, individual or nongeneric reactions, as contrasted to old, inborn or species reactions. Any of these adjectives may suitably be affixed to the reaction, but Pavlov, most impressed by their dependence on many conditions, both in formation and in perpetuation, attached to them the adjective "conditioned." He emphasized that it is in their "conditionality" that these reactions contrast most sharply with more stable, older, inborn or species reactions which, as a group, he called "unconditioned."

The fluidity of the conditioned response is further revealed by the fact that when the conditioned stimulus on which it is based fails to be linked with the stimulus which evokes the unconditioned reaction, the response, which may until that time have been regular enough to be predicted, now gradually falls off and eventually, if coupling does not take place again, entirely disappears.

For the formation of a conditioned response three factors are essential: 1. The animal must have a cerebral cortex. 2. The receptor end-organs, the afferent pathways and the efferent apparatus must be intact. 3. A hitherto inconsequential stimulus must precede and overlap in time the presentation of a second stimulus which elicits an inborn reflex.

The unconditioned responses involving glandular activity are especially useful for experimental purposes, and of these, because of technical convenience, the salivary reflex has most often been chosen. The salivary reflex to food is an old, established, relatively fixed and stable reflex which is elicited by stimulating the mucous membranes of the mouth with various nutritive or rejectable substances. For example, when the giving of food is preceded by the ringing of a bell, this previously inconsequential stimulus takes on the character of a symbol or signal, and after several repetitions in combination with the food (now the significant biologic object which evokes the inborn reaction) gives rise to responses which differ only quantitatively from those resulting from the food itself.

The procedure of giving the second stimulus which evokes the unconditioned response is referred to as reenforcement, since it supports or substantiates the delicate and dependent conditioned response. Thus, in the case of the conditioned stimulus just mentioned, the bell is said to be reenforced when it is coupled with food and, conversely, to be nonreenforced when not thus coupled.

In addition to a reaction to a reenforced conditioned stimulus, a reaction of differentiation may be developed. This reaction results from the ability to distinguish between stimuli which often resemble one another closely yet differ in that one is accompanied by the unconditioned stimulus (which evokes the unconditioned response) while the other is not.

A conditioned stimulus which regularly produces a response gradually fails to do so when it is no longer reenforced. Such a conditioned response is said to have become extinguished. However, although the stimuli fail to elicit the type of response that follows reenforcement, they are not without effect on the behavior of the organism. Thus, when produced just before or with reenforced conditioned stimuli which regularly evoke responses, the latter fail to evoke any response or their influence is much reduced. These nonreenforced stimuli have consequently been referred to as negative conditioned stimuli.

Although the disturbance set up by this type of nonreenforced stimulus is superficially less effective, it is highly active in the sense in which a brake applied to a revolving wheel is "active." The contrasting reactions produced by stimuli followed by an unconditioned stimulus and by stimuli not followed by an unconditioned stimulus may be expressed as opposites in the behavior of the animal. Either type can be significant to the animal's adaptability in nature, the former by increasing the reactivity of the organism, the latter by decreasing it.

It may be inferred that a function which enables an animal to sustain or protect itself because it can anticipate significant biologic events by reacting to symbols or signals formed by previously inconsequential stimuli must inevitably influence all the other functions. Its importance becomes evident when it is appreciated that every unconditioned reaction (inborn reflex) may become coupled with some external stimulus which may then determine its check or release. On the other hand, it does not follow that inborn responses are always dominated by the newer function; although strongly influenced, they still maintain their independence.

In other words, the conditioned response through its influence on all other responses of the organism makes possible its adjustment to an ever-changing environment in which the same stimulus takes on at different times an entirely different significance. The inborn reactions may still occur independently, however, as shown by the extension of the leg that follows the sudden stretching of the patellar tendon (knee jerk) in the intact animal. The independent action may be at times to the advantage of the animal and at other times to its disadvantage. It is apparent that conditioned stimuli do not always evoke a response which exerts an "inhibiting" effect on the inborn response; they incite to greater activity as well as hold in check.

The quality of responding to the signals, signs or symbols presented by numerous stimuli which have been substituted for a significant biologic experience may be looked on as the unique expression of the highest type of integrative function. This quality, termed "signalization" (Pavlov) or "symbolization" (A. Meyer), is the common denominator of all conditioned responses, which may differ enormously in complexity and range, depending on the experience and structural equipment of the animal form investigated.

On these fundamental observations and conclusions the experiments presented in this paper were based. The conditioned response was taken as an expression and test object of the highest integrative function, and the defining qualities just briefly reviewed may be summarized as follows: 1. The conditioned response is the reaction which occurs during the period in which only the symbol is present and before the giving of the stimulus which sets off the inborn or species reflex. 2. It may become weak or disappear should the symbol no longer be coupled with food or with any other stimulus eliciting an inborn reflex. 3. In contrast to the positive type of response, a reaction of differentiation may be developed. This differentiation may be defined as the ability to distinguish between symbols which, although perhaps closely resembling the positive, differ essentially in that they are not accompanied by the stimulus which sets off the inborn or species reflex. 4. These higher integrative functions exert a significant influence on the lower integrative functions.

METHOD

The method used was that developed by Pavlov for the study of conditioned responses. The details of the method of salivary transmission, recording and production of stimuli were modified in an attempt to attain more constant readings and to reduce the errors.

Dogs were used in the experiments. A salivary fistula was produced on each dog's left cheek by dissecting the ampulla of Stenson's duct and everting it so that it drained on the outside of the cheek. Thus all the saliva produced in one parotid gland could be collected by placing a glass cup over the outlet of the duct. Such a glass cup was connected by means of rubber and copper tubing to a manometer about 2 meters distant and situated outside the chamber in which the dog stood during the experiment. The entire conduction system was filled with water, and near the dog was a salivary reservoir which collected most of the saliva and prevented clogging of the copper tubing.

The animal was placed in a chamber constructed in such a way that the experimenter was able to control the environmental circumstances. It was in principle a sound-proof compartment with an inner chamber, measuring 2 by 2 by 2 meters, and with walls 30 cm. thick. In this manner the light, temperature, sound and touch were largely controlled by the experimenter. The animal stood on a platform in front of an automatic food box so built that the experimenter could at a desired moment present a standard article of food to the dog.

The animal was tied by a strap from its collar but was otherwise not bound or supported except in the experiment with drugs. The feet and body were free to move about, but the dog could not get out of the operator's field of vision because of the light leash.

On the wall of the inner chamber were buzzers, metronomes, lights, etc., used as signals; all these signals were controlled from the operator's keyboard.

A small aperture in the wall made it possible to observe the animal during the period before and after the stimulation. The salivary production was measured directly by a manometer and recorded by means of an electric drop recorder. The use of tape and markers made possible a complete graphic record of the time when the stimulus was begun, the amount of saliva produced before the food was presented, the amount present when the food was given and, if desired, the amount produced after the food had been given.

The conditional response to the bell was developed as follows: The dog was placed in the chamber, and after a short period the bell was sounded and allowed to ring for ten seconds. At the end of that time the food was automatically presented in front of the dog. The bell continued to ring without interruption for another twenty seconds, ringing thirty seconds in all. This procedure was repeated again and again; the bell sounded at from four to five minute intervals and alternated with another stimulus, such as the sound of a metronome beating sixty times per minute or a bubbling sound; all the sounds were accompanied by the presentation of food. Generally after from ten to twenty repetitions there was a secretion of saliva as soon as the bell started to ring and before the food was given. After twenty or more repetitions the response became relatively constant. In this manner conditioned responses to the stimulus of a bell, a bubbling sound, the sound of a metronome beating 60 times per minute and a light were developed.

When moderately large and constant responses to these stimuli were being obtained a differentiation was developed by introducing as a stimulus the sound of a metronome beating 140 times per minute, as contrasted to the sound of one beating 60 times, which was always coupled with presentation of food. The sound of the metronome with 140 beats per minute was never coupled with presentation of food. At first the response to this new, nonreenforced stimulus was the same as that to the stimulus coupled with the offering of food, but after about forty presentations of the stimulus without food the stimulus no longer elicited the salivary flow. The nature of this type of reaction is dicussed later.

The experiments were performed at approximately the same hour daily, Sundays excepted. The animals were fed and exercised at about the same time, and the conditions outside the experimental chamber were kept as nearly constant as possible.

Attention is called to the error of ± 15 cu. mm. in the measurement of the saliva; it was due chiefly to the movement of the column of fluid in the manometer resulting from the movement of the dog's head.

EXPERIMENTAL ANIMALS

The experiments were performed on two dogs. Since the type of animal is a factor in the response under any given set of circumstances, a few words of description are necessary to a proper evaluation of the observations.

The first dog (Kompa) was a long-nosed, large-pawed female mongrel of the yellow, short-haired variety, resembling a bloodhound, and weighing 25 Kg. It

was restless, active, capricious, friendly and highly investigative. It barked a little at times, and although seldom aggressive in seeking a quarrel, it fought vigorously when attacked. Positive conditioned reactions were readily developed, and the response was fairly constant. Differentiation was not as easily elaborated, but when ultimately developed it was fairly constant under proper conditions. Under unusual activity, hunger or illness of any variety it became imperfect. In the chamber during the preexperimental period the animal commonly remained standing quietly upright on all fours with the eyes wide open and the head erect. At the beginning of each experiment it usually jumped on the platform with great alacrity. A striking feature was the apparent inability of this animal to develop complete differentiation without immediately going to sleep. The "sleep" was usually of short duration and did not interfere with the progress of the experiments.

With the exception of two months in 1930, the dog remained in the experiment for two years without showing any failure in the intensity or constancy of the response. Such variations as did occur were induced by the operator or by transient illness. All the tables included in this report are taken from protocols on this dog.

The second dog (Curley) was a gray, long-haired male mongrel of the spaniel variety, weighing about 10 Kg. It was active, lively and friendly and barked considerably during activity. It avoided quarrels and usually retreated from engagement when attacked. Acquired reactions were readily developed and remained fairly constant. Differentiation was not attempted. For the purpose of these experiments this dog was not completely satisfactory because the parotid saliva measured was but a small fraction of the total saliva produced. Although the absolute amount was constant it was so small that the error of the method became disproportionately great. Therefore, while the observations on this animal were useful in relation to those on the first dog, they were never accepted as conclusive. It is, however, interesting to note that the results of the experiment on the two dogs differed in quantitative aspects only.

OBSERVATIONS

Control Experiments.—In order to determine the effect of the chemical substances used a series of average control responses were first developed. In the manner described, conditioned responses to the following stimuli were elaborated: the ringing of a bell, a bubbling sound made by passing a stream of air through a bottle of water near the dog's head, the sound of a metronome with 60 beats per minute and a light flashing at a frequency of 60 flashes per minute. In each case the stimulation preceded by ten seconds the presentation of food and continued for twenty seconds during and after the latter procedure. As a differentiated stimulus a metronome beating with a frequency of 140 per minute and never coupled with food was used, and the sounding was continued for sixty seconds. In this instance the readings were made at the end of each period of ten seconds during the sixty seconds in which the metronome sounded.

After many repetitions of the stimuli independently and in changing combinations, a given combination of stimuli was selected. Thereafter the stimuli always followed each other in a definite sequence. The order was: bell, metronome (140 beats per minute), bubbling sound, metronome (60 beats per minute), flashing light and the bell again. This pattern was repeated ninety-one times. At first there were marked fluctuations in the magnitude of the responses, but on further repetition the response became more constant. The average response to the various stimuli was based on from thirty-one to fifty relatively stable responses.

The responses for the control period are shown in table 1. The bell and the bubbling sound elicited a greater response (222 and 231 cu. mm.) than did the other two stimuli. The sound of the metronome with 60 beats per minute produced a response next in order of strength (189 cu. mm.), and the flashing light was the weakest of the reenforced stimuli, producing a secretion of 151 cu. mm. of saliva. The sound of a metronome with 140 beats per minute usually elicited little or no salivary response.

In approximately from 69 to 87 per cent of the repetitions the responses associated with the reenforced stimuli fell within a range of 110 cu. mm. In about from 73 to 79 per cent of the repetitions the nonreenforced stimulus elicited a response of less than 15 cu. mm. From 13 to 31 per cent of the responses were outside of the limits mentioned. The distribution is graphically portrayed. The degree of probability that a given stimulus will elicit a given response can, therefore, be determined from an examination of table 1.

With the reenforced stimuli the general activity as quantitatively approximated by the crude method of observing the animal through the porthole in the experimental chamber roughly paralleled the salivary response.[1] (This is by no means always true.) The average or usual response for the reenforced stimuli was as follows: The dog stood quietly and erect before the food box, usually looking at it or over it. The eyes were well opened, the ears half erect; the animal did not support itself by resting any part of the body on the stand nor did it pull, scratch or jump about on the platform. The breathing was regular and slightly rapid. During the period of stimulation there was a quick turn of the head toward the source of the stimulus (orientation), followed by a turning of the head toward the food box and by a slight step forward with the eyes even more widely opened. The conditioned flow of the saliva usually preceded by several seconds the movement toward the box. When the food was presented, the head quickly bent forward, and the biscuits were rapidly eaten. Then the dog assumed the usual attitude.

The behavior of the dog before the presentation of the nonreenforced stimuli was similar to that described before the presentation of the reenforced stimuli. However, at the sound of the metronome (140 beats, nonreenforced) the head was turned slightly in the direction of the sound and then fell forward, often hanging low, and after from nine to ten seconds it was supported on the box. The eyes were closed, and the animal squatted on its haunches, leaning against the wall and the food box. The breathing was slow and dull. This was called "sleep" because of its resemblance to the condition described by that term and for want of a more objective description and definition of "sleep."

In the observations on the administration of drugs, the action of the drug was determined as follows: The agent was administered, and the responses to the various standard stimuli were determined. These responses were then considered in terms of the probable spontaneous variations under control conditions. If the probability that the response would occur spontaneously was small it was inferred that the unusual reaction resulted from the effects of the drug. In other words, if in a small number of the control observations the animal produced 220 cu. mm. of saliva in response to a standard stimulus whereas after the administration of the drug 340 cu. mm. of saliva was produced much more frequently, this increased secretion could be attributed to the effects of the drug.

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1. The salivary response to the metronome beating 140 times per minute in the control series fell within the limit of error of the apparatus (15 cu. mm.) and is considered negligible in this case.

TABLE 1.—*Summary of Control Experiments* *

Signals	Bell (R)	Metronome (140 beats per minute) (N)	Bubbling sound† (R)	Metronome (60 beats per minute) (R)	Light (flashed 60 times per minute (R)	Metronome (140 beats per minute) (N)	Bell (R)
Total repetitions	238	264	70	138	127	264	238
Total repetitions in combination	91	91	91	91	91	91	91
Total repetitions in stable combination	42	41	31	50	40	44	38
Amount of saliva in cubic millimeters	0- 50= 0= 0% 50-100= 2= 4.8% 100-150= 2= 4.8% 150-200= 9=21.4% ‡200-250=13=31.0% 250-300=12=28.5% 300-350= 4= 9.5% 350-400= 0= 0%	0 =18=44% ‡0- 15=12=29.3% 15- 30= 5=12.2% 30- 50= 4= 9.7% 50- 70= 2= 4.8% 70-400= 0= 0%	0- 50= 0= 0 50-100= 1= 3.2% 100-150= 2= 6.4% 150-200= 6=19.3% ‡200-250=11=35.5% 250-300= 9=29.0% 300-350= 0= 0% 350-400= 0= 0% 400-410= 2= 6.0%	0- 50= 0= 0% 50-100= 3= 6% 100-150= 8=16% ‡150-200=15=30% 200-250=19=38% 250-300= 3= 6% 300-350= 1= 2% 350-400= 1= 2% 400-410= 0= 0%	0- 50= 1= 2.5% 50-100= 1= 2.5% 100-150=18=45.0% ‡150-200=14=35.0% 200-250= 5=12.5% 250-300= 1= 2.5% 300-350= 0= 0% 350-380= 0= 0%	0 =25=48.0% ‡0- 15=14=27.0% 15- 30= 9=17.3% 30- 50= 3= 5.8% 50- 70= 0= 0% 70-110= 1= 1.9% 110-400= 0= 0%	0- 50= 0= 0% 50-100= 0= 0% 100-150= 6=15.8% ‡150-200=14=36.9% 200-250=11=29.0% 250-300= 4=10.5% 300-350= 2= 5.3% 350-400= 1= 2.6%
	‡180-290=29=69%	‡0-15 (incl.)=30=73.3%	‡180-290=24=77%	‡130-260=38=76%	‡100-220=37=92.5%	‡0-15(incl.)=39=75%	‡140-240=27=71.0%
General reaction	++	±S	++	++	+	±S	++
Response in cu.mm. of saliva:							
Minimum response	180	0	180	130	100	0	140
Average response	222	9 (0)	231	189	151	11 (0)	200
Maximum response	290	15	290	250	220	15	240

* In the experiments the experimental error equaled ±15 cubic millimeters; the time interval between stimuli was from four to six minutes; the experiments were performed from 1:30 to 3:00 p.m. The following symbols are used in this and in the following tables: S indicates sleep; ±S denotes a state of lethargy to sleep in which the dog squatted, resting the head on the box; ± denotes drowsiness, a lethargic state with the eyes half shut, the animal leaning against the apparatus; + denotes a quiet attitude, drooping head, open eyes and a standing or squatting posture; ++ indicates that the dog stood erect, with eyes wide open and ears half erect; the posture was upright and the movements were quick; +++ indicates that the dog moved about, was restless and whined; ++++ indicates that the dog was very restless, pulled on the harness or jerked off the apparatus, whined and barked. R indicates reenforced stimuli; N, nonreenforced stimuli.

† The "bubbling sound" was produced by passing air through water.

Before the action of the drug was tried a preliminary control period of several days preceded the experiment, to insure against an error of interpretation due to a temporary and "spontaneous" change in the responses of the animal. The observations made during this period coincided with those obtained in the average and during the longer control period. This "control" gave a stable basis for comparison and, what is more important, furnished a better conception of the range of probability of a given response following the stimulus, so that fewer experiments with drugs were necessary.

It was essential to keep the experiments with drugs at a minimum for the following reasons: 1. Each experiment testing the action of a drug required that the responses be measured repeatedly over many hours. This meant that the animal had to spend from five to seven hours of the twenty-four in the experimental chamber. 2. There was a slight risk to the life of the animal with each intoxication. 3. There was danger that unusual responses would develop as a result of repeated punctures or enemas given just before the animal entered the experimental chamber, and such alterations in responses would complicate the results and make it difficult to interpret the effects of the drug.

TABLE 2.—*Effect of Repeated Determinations at Short and Irregular Intervals* *

Stimulus		Control Average			Experiment of June 26				
		Minimum	Mean	Maximum	2:05 P.M.	8:18 P.M.	9:41 P.M.	11:12 P.M.	General Reaction
Bell	R	180	222	290	182	273	222	271	++
Metronome (140)	N	0	9	15	0	0	0	0	S
Bubbling sound	R	180	231	290	287	255	196	204	++
Metronome (60)	R	130	189	250	209	209	193	169	++
Light (60)	R	100	151	220	164	127	?	118	+
Metronome (140)	N	0	11	15	0	0	0	0	S
Bell	R	140	200	240	238	191	184	173	++

* The salivary production was measured in cubic millimeters. The same symbols are used as in table 1.

As a result of these considerations we adopted the procedure of performing the maximum number of preliminary control experiments compatible with the maintenance of stable responses, and of following these experiments by the minimum number of consistent tests for the action of the substance under consideration.

It was also necessary to control the effect of the repetition of observations, i.e., from five to seven periods of detention in the camera within twenty-four hours. Furthermore, the fact that many of the observations were made late at night—at an hour unusual for the animal—possibly complicated the results. After the experiments with each drug were completed a further series of measurements was made on another day to determine the effect of the procedure. The dog was treated as though a drug was to be administered, and the responses were measured at irregular intervals during the next twenty hours. If the responses were then stable, one could infer that they had not been influenced by the procedure itself.

As is shown in table 2, the salivary production was always within the range of the average, although there was a slight decrease toward the end. It is therefore likely that such alterations in the responses as were observed after the administration of the drug were not due to the extraneous circumstances of the experimental procedure itself.

Experiments with Caffeine Sodiobenzoate.—Control observations on the day preceding the first experiment with caffeine sodiobenzoate showed the conditioned response to be generally lower than usual. This was accepted as satisfactory. Caffeine sodiobenzoate was injected intramuscularly in the amount of 0.016 Gm. per kilogram, or a total of 0.4 Gm. The injection was given after the animal

TABLE 3.—*Observations on the Effect of Caffeine Sodiobenzoate* *

Stimulus		Control Salivary Production: Minimum	Average	Maximum	April 25	General Reaction
Bell	R	180	222	290	218	++
Metronome (140)	N	0	9 (0)	15	0	S
Bubbling sound	R	180	231	290	246	++
Metronome (60)	R	130	189	250	233	++
Light (60)	R	100	151	220	187	+
Metronome (140)	N	0	11 (0)	15	0	S
Bell	R	140	200	240	233	++

April 29, 2:20 p.m. Caffeine Sodiobenzoate, 0.4 Gm. Intramuscularly

Time	Stimulus		Latent Period†: Secretory Response	Latent Period†: Motor Response	Salivary Production	General Reaction
2:28 p.m.	Bell	R	2	3	227	++
2:33	Metronome (140)	N	10	—	27	++
2:38	Bubbling sound	R	2	3	196	++
2:43	Metronome (60)	R	1	2	256	+++
2:48	Light (60)	R	—	—	?	
2:53	Metronome (140)	N	9+	—	73	+++
2:58	Bell	R	1	2	246	+++
3:40	Bell	R	1	2	387	++++
3.45	Metronome (140)	N	10	—	20	++
3:50	Bubbling sound	R	1	2	322	+++
3:55	Metronome (60)	R	2	3	258	+++
4:00	Light (60)	R	1	—	273	+++
4:05	Metronome (140)	R	—	—	9	±
4:10	Bell	N	1	2	265	++
8:10	Bell	R	2	4	209	++
8:15	Metronome (140)	N	10	—	16	±S
8:20	Bubbling sound	R	1	2	364	++++
8:25	Metronome (60)	R	2	9	282	+++
8:30	Light (60)	R	2	—	218	+++
8:35	Metronome (140)	N	10	—	51	+++
8:40	Bell	R	2	4	227	++

April 30 (20 Hours Later)

4:05 p.m.	Bell	R	2	3	255	++
4:14	Metronome (140)	N	—	—	0	S
4:19	Bubbling sound	R	3	4	273	+
4:24	Metronome (60)	R	3	4	186	+
4:29	Light (60)	R	4	—	127	+
4:34	Metronome (140)	N	10	—	20	±S
4:39	Bell	R	2	3	206	++
4:44	Metronome (140)	N	—	—	0	S

* The salivary production was measured in cubic millimeters. The same symbols are used as in table 1.

† In this column the minus sign indicates that no response occurred within ten seconds.

had been prepared for the experiment with head-gear in place so that the first observation could be made a few minutes later.

A protocol has been tabulated (table 3). Immediately after the administration of the caffeine sodiobenzoate, the responses were slightly increased, possibly because of the procedure of injection. At 2:53 p. m., twenty-six minutes after the injection, the response to the metronome (140 beats per minute) was raised to 73 cu. mm. This was the earliest effect of the drug seen in the protocol described, although the metronome beating 60 times per minute just preceding the adminstration of the drug also evoked an increased response. At 3:40, one hour

and thirteen minutes after the injection, the stimuli were repeated. The responses throughout were increased. However, the effect was more apparent in the response to the reenforced stimuli than in that to the nonreenforced stimuli. In fact, during this phase of its action the caffeine sodiobenzoate seemed to improve the differentiation slightly.

The latent period or reaction time, i.e., the time between the presentation of the stimulus and the reaction of salivary secretion and of movement toward the food box, was determined in most experiments. The effects of caffeine sodiobenzoate on the latent period are shown in table 4. The latency is usually shortened. This shortening of the period is more evident during the first two hours following the administration of the caffeine sodiobenzoate and less so six hours later. Table 4 shows that in approximately 80 per cent of the observations the latency of secretion in reaction to the standard stimuli after the administration of caffeine sodiobenzoate occurred in the first two seconds. This contrasts with the 10 per cent that occurred in the first two seconds in the control series. The effect is particularly evident in the case of the stimuli that commonly had a longer latency

TABLE 4.—*Period of Latency Between Stimulation and Response* *

	Before Caffeine Sodiobenzoate				After Caffeine Sodiobenzoate			
	Number of Observations		Percentage of Occurrence		Number of Observations		Percentage of Occurrence	
Time in Seconds	Secretory Response	Motor Response	Secretory Response	Motor Response	Secretory Response	Motor Response	Secretory Response	Motor Response
1	5	0	1.6	0	14	0	42.4	0
2	27	0	8.9	0	13	8	39.4	23.6
3-7	264	155	87.4	57.0	6	17	18.2	50.0
7-10	6	117	1.9	43.0	0	9	0	26.4
Total	302	272			33	34		

* The following stimuli were used: a bell, a bubbling sound, a metronome beating 60 times per minute and a light flashed 60 times per minute.

(flashing light), and is more apparent on the latency of the salivary secretion than on that of the motor reaction. The method of observing the latter is very crude and cannot be accepted too literally. The more subtle movements of the animal toward the food box can hardly be accurately timed. Short reaction time in most instances accompanied an increased secretion of saliva.

Sleep, which usually accompanied the sound of the metronome beating 140 times per minute, was completely dispelled. During the entire period of the experiment the animal was unusually quick in its movements; the head was held somewhat higher; the ears were raised, and the eyes were wide open. Following the stronger stimuli there was considerable restlessness with quasipurposive movements, more rapid breathing and occasional outbursts of panting. As mentioned, the movements of the head both in the initial turning of the head toward the source of the stimulus (orienting movements) and the later movement toward the food box (conditioned movements) were extremely rapid. The only change noted during the sounding of the metronome (140 beats per minute) was a slight lowering of the head and a collapse of the erected ears. Never did the animal rest its head on the box or lean against the supports.

Observations continued to be made every four or five hours after the injection over the next twenty-seven hours and were repeated once each day for the next few days. Six hours after the injection the effect of the drug was still apparent.

At no time was there a decrease in the responses. (As a fact, the values during this period returned to the low level observed just before the caffeine sodiobenzoate was administered.) Sleep with and after the sounding of the metronome at 140 beats per minute recurred about twenty-seven hours after the injection.

During the height of the reaction following the administration of the drug all the salivary responses were increased over 20 per cent, and about half of them were increased to a degree not commonly seen in spontaneous variations from the average (chart 1). The motor activity roughly paralleled the degree of increase in the salivary responses.

Five experiments with caffeine sodiobenzoate were performed. In one experiment, which was carried out during estrus, the animal was restless and overactive. It was observed that the effect of the drug on the response to the nonreenforced

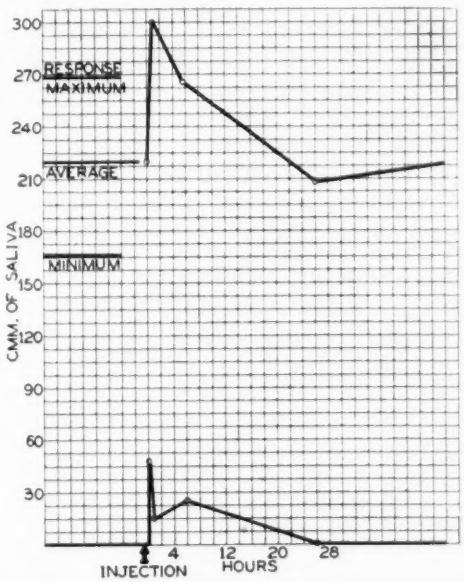

Chart 1.—Composite graphic representation of the effect of caffeine sodiobenzoate. Caffeine sodiobenzoate (0.4 Gm.) was injected intramuscularly (time indicated by the arrow). During the subsequent thirty minutes the responses of the dog to the reenforced conditioned stimuli (bell, bubbling sound, metronome [60 beats per minute] and light [60 flashes per minute]), represented by the upper line, were unchanged from the level for the control period. Beginning then, however, the responses increased. Thus, the response to the nonreenforced stimulus (metronome [140 beats per minute]) represented by the lower line averaged 50 cubic millimeters of saliva, in contrast to the zero response observed during the control period. One hour and twenty minutes after the injection the animal was overalert, active and highly responsive to all conditioned stimuli. At this point the reaction to the metronome beating 140 times per minute was still increased. Measurements made four and one-half hours later showed that the animal gave responses approximating the maximum control level. Twenty hours after the first observation responses to all the stimuli had approached the original level.

stimulus was greater than the effect on the response to the reenforced; the latter response was actually somewhat reduced. This variation may have been related to the initial highly responsive state of the animal. In this instance after the administration of caffeine sodiobenzoate the dog was extremely restless and overactive. With this exception the results in all experiments were similar; sleep was dispelled in all instances.

Experiments with Sodium Iso-Amylethyl Barbiturate.—As in the case of the caffeine sodiobenzoate, the animal was prepared for the measurement of salivary flow before the drug was injected. Small and large doses were given intraperitoneally in a 10 per cent aqueous solution. The first measurement was made as soon thereafter as was technically possible. The large doses induced a prompt and relatively deep narcosis, and the small doses produced a light narcosis or sleep which was of short duration. The action on the conditioned response was investigated for both dosages. A larger dose was given first (table 5). An injection of approximately 30 mg. per kilogram, or a total of 725 mg., was given at 1:58 p. m., and immediately thereafter the animal was lifted in place on the platform. Unfortunately, owing to technical difficulties the first reading could not be made until 2:10 p. m., although during the first two or three minutes after the injection the animal was definitely overactive. By the time the reading was made the animal had become lethargic and showed little response to the usual stimuli. In fact, no salivary responses were obtained until 8:56 p. m., six and three-quarters hours later, although the entire series of stimuli were given at 4:45 and at 6:45 p. m.

From 2:10 until 4:57 p. m. the animal did not take the food, and not even the unconditioned response could be obtained by actually placing the food in its mouth. However, although both the conditioned and the unconditioned reflexes had entirely disappeared, a slight quivering or even a slight elevation of the ears could be detected when the strong sound stimuli were presented. These orienting movements were the last to be submerged and the first to reappear. Sometimes they were strong (in fact more evident than usual) before the conditioned responses had attained any degree of stability and grew weaker as the latter regained their former strength until, with the reestablishment of the conditioned responses, they were of the usual weakness and entirely secondary to the movements associated with the conditioned responses. At 4:57 p. m., nearly four hours before the conditioned response reappeared, the unconditioned response to the food returned and reached its full strength at once.

The conditioned response to the bell (the loudest stimulus) was the first to return and that to the metronome (60 beats per minute) the second. The animal still remained asleep between stimuli, and during and after the sounding of these two stimuli moved just enough to eat the food. Sleep returned at once after the feeding.

At 12:25 a. m., about eleven hours after the injection, responses were obtained to all the test stimuli except to the light. At 3:40 a. m., about fourteen hours after the injection, the bell, the simulus of greatest intensity, which throughout had elicited the greatest responses, caused 382 cu. mm. of saliva to be secreted. This amount far exceeded the "control" level and approximated that elicited by the bell at the height of action of the caffeine sodiobenzoate. The responses to the sound of bubbling and of the metronome (60 beats per minute) at this time, although considerably higher, did not equal the responses to the bell. The determination made twenty-four hours after the injection showed that the general responsiveness was higher than the preexperimental average.

TABLE 5.—*Observations on the Effect of Sodium Iso-Amylethyl Barbiturate* *

Control Salivary Production

Stimulus		Minimum	Average	Maximum	March 11	March 12	March 16	March 17	General Reaction
Bell	R	180	222	290	237	287	275	233	Alert
Metronome (140)	N	0	9 (0)	15	0 (?)	0	0	22	Quiet sleep?
Bubbling sound	R	180	231	290	136	122	118	175	Alert
Metronome (60)	R	130	189	250	184	204	127	142	Quiet alert
Light (60)	R	100	151	220	173	133	109	124	Quiet alert
Metronome (140)	N	0	11 (0)	15	0	0	0 (?)	0	Sleep
Bell	R	140	200	240	178	164	122 (?)	173	Alert

March 19, 1:58 p.m.: Sodium Iso-amylethyl Barbiturate, Intraperitoneally
Dose: 7.25 Mg. in 10 per Cent Aqueous Solution

Time	Stimulus		Latent Period† Secretory Response	Latent Period† Motor Response	Salivary Response	General Reaction
2:10	Bell	R	—	—	0	Slept heavily
2:13	Metronome (140)	N	—	—	0	Slept heavily
2:19	Bubbling sound.	R	—	—	0	Slept heavily
2:20	Metronome (60).	R	—	—	0	Slept heavily
2:24	Light (60)	R	—	—	0	Slept heavily
2:27	Metronome (140)	N	—	—	0	Slept heavily
3:13	Bell	R	—	—	20 (?)	Slept heavily
3:15 to 4:45 p.m. dog asleep						
4:45	Bell	R	—	—	0	Slept; did not eat
4:49	Metronome (140)	N	—	—	0	Slept; did not eat
4:57	Bubbling sound.	R	—	—	0	Slept; awakened by bubble; staggered
5:02	Metronome (60).	R	—	—	0	Went to food only when it appeared
5:07	Light (60)	R	—	—	0	Went to food only when it appeared
5:12	Metronome (140)	N	—	—	0	Slept throughout
5:12 to 6:45 p.m. dog asleep						
6:45	Bell	R	—	—	0	Awakened by stimulus
6:49	Metronome (140)	N	—	—	0	Head on box; unsteady hindlegs; slept
6:54	Bubbling sound.	R	—	—	0	Awakened by stimulus; ate; hung head
6:59	Metronome (60).	R	—	—	0	Awakened by stimulus; ate; hung head
6:59 to 7:11 p.m. dog asleep						
7:11	Bell	R	—	—	0	Awakened by stimulus but unsteady on legs; slept
7:16	Metronome (140)	N	—	—	0	Slept
7:21	Light (60)	R				Awakened by stimulus; did not eat; slept
7:21 to 8:56 p.m. dog asleep						
8:56	Bell	R	7	—	82	Slept heavily
9:01	Metronome (140)	N	—	—	0	Slept heavily
9:05	Bubbling sound.	R	—	—	0	Slept heavily
9:10	Metronome (60).	R	9	—	27	Slept heavily
9:15	Light (60)	R	—	—	0	Slept heavily
9:25	Metronome (140)	N	—	—	0	Slept heavily
9:30	Bell	R				Slept heavily
A.M. March 20						
12:25	Bell	R	6	—	200	Alert
12:30	Metronome (140)	N	—	—	0 (9)	Slept
12:35	Bubbling sound.	R	8	—	82	Slept; awakened by stimulus; ate; slept
12:40	Metronome (60).	R	7	—	113	Slept; awakened by stimulus; ate; slept
12:45	Light (60)	R	—	—	0	Slept; awakened by stimulus; ate; slept
12:50	Metronome (140)	N	—	—	0	Slept
12:55	Bell	R	—	—	0	Slept; awakened by stimulus; ate; slept
3:40	Bell	R	2	4	382	Alert; overactive; restless
3:45	Metronome (140)	N	—	—	0	Slept
3:50	Bubbling sound.	R	3	5	169	Slept; awakened by stimulus; ate; slept
3:55	Metronome (60).	R	4	4	127	Slept; awakened by stimulus; ate; slept
4:00	Light (60)	R	—	—	0	Slept
4:05	Metronome (140)	N	—	—	0	Slept
4:10	Bell	R	—	—	0	Slept
P.M. March 20						
1:12	Bell	R	5	5	307	Alert; did not sleep; overactive
1:17	Metronome (140)	N	—	—	—?	Slept
1:21	Bubbling sound.	R	2	1	318	Alert; overactive
1:26	Metronome (60).	R	5	—	184	Alert; overactive
1:30	Light (60)	R	6	5	93	Alert; overactive
1:35	Metronome (140)	N	—	—	0	Slept
P.M. March 21						
1:36	Bell	R	3	4	282	Alert; overactive
1:57	Bell	R	3	4	227	Erect; quiet; quick movements
2:02	Metronome (140)	N	—	—	0	Slept
2:16	Bubbling sound.	R	4	6	173	Erect; quiet; quick movements
2:21	Metronome (60).	R	3	6	318	Erect; quiet; quick movements
2:26	Light (60)	R	?	?	173	Erect; quiet; quick movements

* The salivary production was measured in cubic millimeters. The same symbols are used as in table 1.

† In this column the minus sign indicates that no response occurred within ten seconds.

The general activity roughly paralleled the salivary responses. The dog was awake and moderately active at 12:25 a. m., but with the sounding of the bell slept soon after the food had been given and thereafter awoke only with the sound of the bubbling and metronome (60 beats per minute). When the sound ceased it immediately went to sleep again. The situation differed when the metronome beating 140 times per minute was sounded. Each time this stimulus was introduced the animal, if leaning against the box, sagged even more and if standing erect fell against the supports; if the eyes were half open they closed after four seconds, and the animal went into a sleep from which it did not awake until either the bubbling or the bell was sounded again.

At 3:40 a. m. (fourteen hours after the administration of the drug) the new phase began. The animal moved excessively; the salivary response after the bell was greatly increased, the ears were erect; the dog maintained an erect posture; the breathing was rapid, and panting occurred for a minute. This overactive state did not last very long, for with the sounding of the metronome (140 beats per minute) the dog slept again. Ten hours later, or twenty-four hours after the beginning of the experiment, the animal was in a state of overactivity practically all the time except during and after the sounding of the metronome beating 140 times per minute. This sound was always followed by a light, interrupted sleep (table 5).

A dose about half the size of the preceding, namely, 15 mg. per kilogram, or a total of 375 mg., was injected intraperitoneally in two experiments (table 6). In both instances measurements of the responses were quickly obtained before narcosis occurred. The bell evoked a salivary production of 382 cu. mm., similar to that obtained in the first experiment during overactivity following the narcotic phase. This was followed by a loss of all acquired responses; at 2:13 p. m. the response to the metronome beating 140 times per minute was actually greater than that to the bell or the bubbling sound. Withing an hour and a half, however, the responses returned, and their return was in the order of the intensity of the stimuli, the response to the bell and the bubbling sound returning first, that to the metronome next, and that to the light last. In this experiment, as in the first, the reenforced stimulus (metronome, 140 beats per minute) augmented such soporific qualities as were already present. With the small dose the unconditional or inborn reflex was never lost. Furthermore, the secondary increase in responses following the narcotic phase was not observed. As in the first experiment, the orienting movements were stronger during the stage in which the conditioned responses were reduced and grew weaker as the conditioned responses again attained their former magnitude.

After the initial activity, characterized by pulling on the supports,[2] putting the feet on the food box, swinging the head about, treading from one side of the platform to the other and responding with great speed to the sound of the bell, the animal gradually became more and more unsteady on its feet, sat on its haunches, swayed in the support, leaned against the food box, rested its head on the food box and fell into a fitful sleep. From this it roused from time to time and always with the beginning of each stimulus with the exception of the light. All the responses had disappeared within ten minutes of the injection, and sleep began, from which it was difficult to arouse the dog. The animal continued in a stuporous state through the next series of measurements, from 3:22 to 3:46 p. m., but by 6:03 p. m., when the third series was started, the responses were moderately

2. A supporting harness was sometimes used in the narcosis of the experiments with drugs.

strong, and the anmal was active and erect for five minutes following the sounding of the metronome (140 beats per minute). Again the effect was as though the animal had suddenly inhaled a noxious gas or had received a forceful blow on the head. Chart 2 shows a composite curve of the responses to the bell constructed by combining the results of experiments 1 and 2.

TABLE 6.—*Observations on the Effect of Sodium Iso-Amylethyl Barbiturate* *

		Control Salivary Production						
Stimulus		Minimum	Average	Maximum	March 29	March 30	March 31	General Reaction
Bell.....	R	180	222	290	233	226	204	Erect; quiet; quick movements
Metronome (140)	N	0	9	15	0	0	0	Slept
Bubbling sound.	R	180	231	290	280	233	282	Erect; quiet; quick movements
Metronome (60).	R	130	189	250	240	262	245	Erect; quiet; quick movements
Light (60).....	R	100	151	220	142	218	214	Erect; quiet; quick movements
Metronome (140)	N	0	11	15	0	0	0	Slept
Bell.....	R	140	200	240	†	†	313	Erect; quiet; quick movements

April 2, 1:55 p.m.: Sodium Iso-amylethyl Barbiturate, 375 mg. Intraperitoneally

			Latent Period†			
Time, P.M.	Stimulus		Secretory Response	Motor Response	Salivary Response	General Reaction
1:58	Bell.....	R	2	3	382.20	Overactive
2:00	Metronome (140)	N	—	—	0	Quiet
2:04	Bubbling sound.	R	—	—	14	Quiet
2:07	Metronome (60).	R	—	—	0	Unsteady; hanging head
2:10	Light (60).....	R	—	—	0	Unsteady; hanging head
2:13	Metronome (140)	N	9	—	31	Unsteady; hanging head; restless
2:17	Bell.....	R	5	—	9	Unsteady; hanging head; restless
3:22	Bell.....	R	5	—	80	Unsteady; stuporous; slept
3:25	Metronome (140)	N	—	—	0 (7)	Unsteady; stuporous; slept
3:30	Bubbling sound.	R	6	7	100	Unsteady; stuporous; slept
3:34	Metronome (60).	R	6	—	40	Unsteady; stuporous; slept
3:38	Light (60).....	R	—	—	0	Unsteady; stuporous; slept
3:42	Metronome (140)	N	—	—	0	Unsteady; stuporous; slept
3:46	Bell.....	R	7	—	82	Slept
6:03	Bell.....	R	4	5	182	Erect; quiet; quick movements
6:07	Metronome (140)	N	—	—	0	Slept
6:12	Bubbling sound.	R	6	7	132	Quiet; slow movements
6:17	Metronome (60).	R	5	7	146	Quiet; slow movements
6:21	Light (60).....	R	—	—	0	Slept
6:25	Metronome (140)	N	—	—	0	Slept
6:30	Bell.....	R	7	8	149	Erect; quiet; quick movements
A.M. April 3 (15 hours later)						
9:22	Bell.....	R	3	4	213	Erect; quiet; quick movements
9:27	Metronome (140)	N	—	—	0	Slept
9:32	Bubbling sound.	R	5	4	191	Erect; quiet; quick movements
9:38	Metronome (60).	R	4	—	193	Erect; quiet; quick movements
9:44	Light (60).....	R	7	—	118	Erect; quiet; quick movements
9:48	Metronome (140)	N	—	—	0	Slept
9:54	Bell.....	R	3	4	166	Erect; quiet; quick mevements

* The salivary production was measured in cubic millimeters. The same symbols are used as in table 1.

† In this column the minus sign indicates that no response occurred within ten seconds.

In the third experiment the results almost paralleled those obtained in the second. The only feature that was slightly different occurred in the responses during the first part of the narcotic phase when all the responses became about equal instead of ranging themselves quantitatively at a lower level in the order of their original strength.

In the fourth experiment a small and moderate dose of sodio-amyletheyl barbiturate, consisting of 7.5 mg. per kilogram, or a total of 0.1875 Gm., was given. The effect on the responses was far less marked. There was no appreciable

decrease in the salivary responses to the reenforced stimuli and only a slight reduction in the motor activity. However, the effect of the nonreenforced stimulus, (metronome, 140 beats per minute) was definitely greater. As was observed in the recovery after the larger dose was given, the sounding of the metronome at 140 beats per minute caused more pronounced changes than when the same stimulus was used during "control" experiments. Approximately four seconds after the stimulus had started the animal drooped as though suddenly overcome and remained in an unbroken sleep for five minutes, or until the ringing of the bell or the bubbling noise sounded. The sleep then promptly disappeared, and a typical response to the reenforced stimulus was elicited. No effect of the drug could be noted when the animal was observed outside the chamber.

The reaction time for both secretory and motor responses was shorter during the initial period of excitement, but after the onset of the narcotic phase the latency was prolonged. As the period of secondary increase in responses began the latency became shorter. In the experiments in which no such secondary increase occurred the reaction time gradually returned to the usual level.

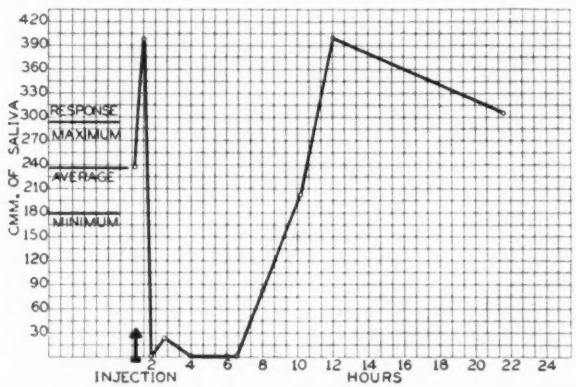

Chart 2.—Composite graphic representation of a series of experiments on the effect of sodium iso-amylethyl barbiturate on the conditioned response to the ringing of a bell. The drug was injected in a 10 per cent aqueous solution (time indicated by the arrow). For a few minutes after the injection the dog was overactive and gave an exaggerated salivary response to the conditioned stimuli. It then became more relaxed and lethargic, went to sleep and gave no appreciable salivary response to any of the stimuli for about five hours. At the end of ten hours the animal could be roused from its stupor and again became overactive, passing through another period of exaggerated responses. This overactive condition persisted for several hours. About ten hours after the dog's rousing from the lethargy the salivary response was still increased in amount over the maximum response observed during the control period.

The effects of sodium iso-amylethyl barbiturate on latency contrasted with those produced by caffeine sodiobenzoate. The caffeine sodiobenzoate shortened the latent period: In 80 per cent of the instances the interval between the stimulus and the onset of the reaction was one or two seconds. The barbiturate administered in moderate or large amounts, with the exceptions mentioned, caused the latency to be prolonged. In approximately 60 per cent of sixty-six observations the latent

period between the stimulus and the onset of the secretion was between eight and ten seconds (control experiment, 2 per cent).

Experiments with Sodium Bromide.—The effects of both small and large doses of sodium bromide were determined. The former were administered first. After the usual preparations for the measurement of saliva had been made, the dog was given an enema containing 120 mg. of sodium bromide per kilogram of body weight in 5 per cent aqueous solution, or a total of 3 Gm. (table 7). Nothing unusual was observed in the responses during the first twenty minutes following the administration of the drug. At the end of that time and after the presentation of the reenforced stimuli the movements became slightly slower; the animal rested its

TABLE 7.—*Observations on the Effect of Sodium Bromide* *

Stimulus		Control Salivary Production			May 25	May 26	General Reaction
		Minimum	Average	Maximum			
Bell	R	180	222	290	109	218	Alert
Metronome (140)	N	0	9	15	0	0	Slept
Bubbling sound	R	180	231	290	213	187	Alert
Metronome (60)	R	130	189	250	196	273	Alert
Light (60)	R	100	151	220	136	154	Alert
Metronome (140)	N	0	11	15	0	0	Slept
Bell	R	140	200	240	254	100	Alert

May 26, 3:05 p.m.: Sodium Bromide, 3 Gm. by Rectum

Time, P.M.	Stimulus		Latent Period†			General Reaction
			Secretory Response	Motor Response	Salivary Response	
3:09	Bell	R	2	3	218	Alert
3:14	Metronome (140)	N	—	—	0	Slept
3:19	Bubbling sound.	R	3	4	182	Slept; ate; slept
3:24	Metronome (60).	R	4	5	169	Slept; ate; slept
3:29	Light (60)	R	4	?	147	Slept; ate; slept
3:34	Metronome (140)	N	—	—	0	Slept
3:39	Bell	R	4	5	133	Alert
5:59	Bell	R	3	4	218	Alert
6:04	Metronome (140)	N	—	—	0	Slept
6:09	Bubbling sound.	R	2	3	227	Alert
6:14	Metronome (60).	R	4	5	173	Alert
6:19	Light (60)	R	3	—	146	Alert
6:24	Metronome (140)	N	—	—	0	Slept
6:28	Bell	R	3	4	223	Alert

* The salivary production was measured in cubic millimeters. The same symbols are used as in table 1.

† In this column the minus sign indicates that no response occurred within ten seconds.

head and even went to sleep for a minute and a half after the bubbling sound, the sound of a metronome beating 60 times per minute, and the flashing of the light, a reaction usually observed only after the sound of the metronome beating 140 times per minute. Four seconds after the presentation of the latter stimulus the dog showed the first evidence of stupor, which promptly progressed to a deep sleep. Uninterrupted sleep continued from 3:34 until 3:39 p. m., when the bell was sounded. At that time the movements were definitely slow, the orienting movements being slightly more continuous and the conditioned movements toward the food box delayed. The latent period between the onset of the ringing of the bell and the production of the first measurable amount of saliva was prolonged. (The average before the administration of the drug was two plus seconds; after the administration it was four plus seconds). The actual salivary production was reduced, although it remained within the average range.

The next series of measurements was begun at 5: 59 p. m., approximately three hours later. No deviation from the average was observed with the possible exception of the reaction to the metronome beating 140 times per minute. Both the speed of onset of sleep and its duration were slightly increased.

Large amounts of the drug were given in subsequent experiments. In an attempt to make the effect of the bromide more apparent, this type of experiment was postponed until an overactive state had spontaneously developed. This occurred in the later stages of the animal's pregnancy. After being prepared in the usual manner the dog was given an enema containing 280 mg. per kilogram (a total of 7 Gm.) of sodium bromide in 5 per cent aqueous solution. The effect was definite although the onset was slow.

The responses, both motor and salivary, were unusually high before the bromide was given. The animal moved about restlessly, whined, panted and pulled on the apparatus. The nonreenforced stimulus gave a response almost as strong as that produced by the flashing light. Besides there was considerable instability since the terminal ringing of the bell gave a response lower than the average response it had produced and out of line with the volume of the other responses. The bubbling sound and the metronome (60 beats per minute) both gave responses far larger than either the initial or the terminal bell.

The enema containing the bromide was given at 3: 52 p. m., and measurements made four and a half hours later showed that with one exception the responses to reenforced stimuli were all lowered. The nonreenforced stimulus (metronome, 140 beats per minute) elicited a very great response, 309 cu. mm., an amount in marked contrast to 45 cu. mm., the response to the terminal ringing of the bell. The weak and strong responses approximated each other, or the weak actually gave more than the strong.

During this series of measurements the motor activity was reduced considerably, although there was a recurrence of the initial restlessness and panting when the metronome beating 140 times per minutes was sounded, with the resultant secretion of 309 cu. mm. of saliva.

At 10: 07 p. m., or about six hours after the administration of bromide, the responses were again determined. Salivary response was elicited only by the strongest stimuli, the initial ringing of the bell, the bubbling sound and the metronome beating 60 times per minute, and even these responses were very small (although in the proper ratio), namely, 45, 45 and 27 cu. mm., respectively. The animal was sluggish and underactive throughout this period, but after the metronome beating 140 per minute was sounded the dog went into a stuporous sleep which was interrupted only long enough to eat the food that accompanied the presentation of subsequent stimuli.

Measurement made seventeen hours later showed that the responses were again greater than the average and that differentiation was poorly maintained.

A repetition of this experiment demonstrated that these results were not to be explained on the basis of the large dose of bromide alone. The following experiment was performed when the initial or control state of the animal was in no way unusual: Two grams of sodium bromide was given per rectum after a satisfactory preliminary period of control observation. The effect on the salivary and motor responses was similar to that in the first experiment. The duration of the action was somewhat longer, and the sleep after the sounding of the metronome with 140 beats per minute came on more promptly and persisted longer. There was more sleep from one to two minutes after the reenforced stimuli, but the differentiation was excellent, and the volume of the salivary responses to

reenforced stimuli was not decreased. No reversal or equalization of responses was noted.

Given in small doses the sodium bromide had little effect on the reaction time of either secretory or motor responses. Even with large doses the latency was usually within the range, although occasionally at the upper limits, of the average.

Experiments with Chloral Hydrate.—The animal was prepared for observation in the manner heretofore described and was then given an enema containing 100 mg. per kilogram, or 2.5 Gm., of chloral hydrate in 5 per cent aqueous solution. The first measurements were made seven minutes later and at three intervals during the next five hours (table 8).

TABLE 8.—*Observations on the Effect of Chloral Hydrate* *

Stimulus		Control Salivary Production: Minimum	Average	Maximum	June 2	General Reaction
Bell	R	180	222	290	118	Alert
Metronome (140)	N	0	9	15	18 (?)	Slept
Bubbling sound	R	180	231	290	182	Alert
Metronome (60)	R	130	189	250	220	Alert
Light (60)	R	100	151	220	138	Alert
Metronome (140)	N	0	11	15	13 (?)	Slept
Bell	R	140	200	240	291	Alert

June 2, 4:10 p.m.: Chloral Hydrate, 2.5 Gm. by Rectum

Time, P.M.	Stimulus		Latent Period†: Secretory Response	Motor Response	Salivary Response	General Reaction
4:17	Bell	R	?	?	282	Alert
4:22	Metronome	N	—	—	0 (9)	Slept
4:27	Bubbling sound	R	3	4	155	Quiet
4:32	Metronome	R	2	3	200	Quiet; slept
4:37	Light	R	3	?	136	Quiet
4:42	Metronome	N	—	—	0 (13)	Slept
4:46	Bell	R	2	2	209	Alert
5:40	Bell	R	2	3	255	Alert
5:45	Metronome	N	—	—	0	Slept
5:50	Bubbling sound	R	3	3	242	Quiet
5:55	Metronome	R	2	3	307	Quiet
6:00	Light	R	2	9	245	Quiet
6:05	Metronome	N	—	—	0	Slept
6:10	Bell	R	2	3	182	Alert

* The salivary production was measured in cubic millimeters. The same symbols are used as in table 1.

† In this column the minus sign indicates that no response occurred within ten seconds.

The results did not differ essentially from those observed following the administration of moderate amounts of sodium bromide or sodium iso-amylethyl barbiturate. The response to the stimuli was not reduced, and sometimes it was slightly raised. The contrast between the responses to reenforced and those to nonreenforced stimuli was accentuated. Sleep after the sounding of the metronome at 140 beats per minute was more promptly induced, less interrupted and of longer duration. There was occasional relaxation with half-closed eyes or sleep for one or two minutes after the reenforced stimuli, but this was superficial and frequently interrupted. The motor activity when the dog was within the chamber was slightly reduced. Before the administration of the drug the dog was erect, quiet and quick in movement with all the reenforced stimuli, and slow and relaxed with the nonreenforced stimuli; after the administration of the drug there was more relaxation throughout, with more resting of the head and far more sleep.

As with sodium bromide, no change in the general behavior of the animal when outside the chamber could be observed.

COMMENT

To indicate the effects of stimuli it is considered expedient to use the purely descriptive and neutral term "threshold." Thus, the phrase "threshold raising" indicates that for a variable period subsequent to the presentation of a given stimulus the salivary responses are reduced, and usually in association with this variation in response there are underactivity and relaxation with semiclosure of the eyes or sleep. Conversely, "threshold lowering" describes the effect of stimuli which are followed by an increase of salivary production, and when this occurs the dog becomes overactive and restless, pants, barks and whines.

In the preliminary analysis of the responses to the standard test stimuli it was noted that the reenforced stimuli, especially those involving stronger salivary responses, appeared to lower the threshold of the highest integrative function so that subsequent stimuli gave greater effects. On the other hand, after the establishment of a differentiation as the result of nonreenforcement of a stimulus, the presentation of that stimulus appeared to raise the threshold so that the responses to subsequent stimuli were less than when they had not been thus preceded. In fact, the rise in the threshold often became so great that the animal failed to respond not only to the reenforced stimuli but to all environmental stimuli and, in addition, seemed, to all outward appearances, to be asleep.

After the administration of caffeine sodiobenzoate the threshold was lowered. Differentiation was poorer during the period shortly after the injection, and apparently before there was much change in the responses to the reenforced stimuli. Furthermore, the sleeplessness is evidence that the nonreenforced stimuli were prevented from becoming as widespread in their effect on the behavior of the animal as was usual after the sounding of the metronome at 140 beats per minute. However, the general increase in the responses to the reenforced stimuli, both motor and salivary, was pronounced and appeared to parallel in time of onset and in degree that produced by the caffeine sodiobenzoate on the responses to nonreenforced stimuli.

The fact that in one experiment the response to the nonreenforced stimulus was greatly increased and that to the reenforced stimulus actually decreased is not to be taken as evidence that caffeine chiefly affects the reaction to the nonreenforced stimuli. A possible explanation for this unusual reaction is as follows: Within certain limits the response to a stimulus is in direct proportion to its intensity. When these limits are exceeded the reaction decreases. The effect of stimuli of tremendous intensity, such as great noises or flashes of light, may be not only to reduce the response to that stimulus but to disturb the reaction

to all subsequent stimuli (Pavlov [3]). Thus if, through administration of caffeine, the threshold is so lowered that the first bell has the effect of an excessively loud stimulus, the salivary response may be reduced. With this exception no decrease in the conditioned response was observed during any phase of the action of caffeine. (The observations recorded here essentially agree with those made by Nikiforovski [Pavlov [4]]).

The action of caffeine is further demonstrated in the course of long experiments in which the animal fails to maintain differences in the size of the acquired responses corresponding to stimuli of different strength. If the responses become weaker or equal and the animal becomes apathetic, the administration of caffeine promptly dispels the apathy, and the responses return to their usual and relative size (Pavlov [5]).

In short, the effect of caffeine on the highest integrative functions is general. The thresholds to both reenforced and nonreenforced conditioned stimuli are lowered to essentially the same degree. Caffeine has a prompt effect on the response to nonreenforced stimuli. It restricts their influence, since the usual let-down in general activity with or without sleep does not occur. Furthermore, it heightens the influence of the reenforced stimuli; that is, by lowering the threshold of the highest integrative functions, it accentuates the effect of threshold-lowering stimuli and lessens the effect of threshold-raising stimuli.

The action of the larger doses of sodium iso-amylethyl barbiturate may be divided into four phases: (1) the phase of initial increase in conditioned responses;[6] (2) the phase of narcosis; (3) the phase of recovery from narcosis, and (4) the phase of postnarcotic or secondary increase in conditioned responses. All the phases were not consistently present. The first phase was very short, owing perhaps to the rapid absorption through the peritoneum. The alteration in the salivary response might easily have been missed unless measurements were made within a few minutes after the injection. The last phase was possibly related to the duration of the narcotic phase. It was absent in the

3. Pavlov, I. P.: Conditioned Reflexes, translated by G. V. Anrep, New York, Oxford University Press, 1927, p. 318.

4. Pavlov,[3] p. 127.

5. Pavlov, I. P.: Lectures on Conditioned Reflexes, translated by W. H. Gantt, New York, International Publishing Co., 1928, p. 356.

6. In the course of anesthetizing several hundred cats for experimental purposes one of us (H. G. W.) observed that following the intraperitoneal injection of sodium iso-amylethyl barbiturate in doses of from 8 to 9 cc. of 1 per cent solution per kilogram of body weight, in the majority of instances the animal, if permitted, ran about, often bumping into obstacles, staggering, falling, and finally, when its legs failed to support it, lay on its side, and within from four to five minutes fell asleep.

experiments in which the narcotic phase was short and was present when the latter was long.

The size of the dose seemed to determine the degree of change in the responses as well as the duration of this change. Probably the rate of absorption of the drug is also a factor.

The initial increase in responses was not limited to the salivary response. The general motor overactivity was clearly apparent from the behavior of the dog.

The initial phase was followed by a second phase in which the threshold was so much higher that not even the strongest conditioned stimuli produced an effect, although the unconditioned stimuli still elicited a salivary response for a brief period. It is of interest that the orienting movements were present in a diminished form after both the conditioned and the unconditioned responses had disappeared. At the end of varying lengths of time the functions returned in the reverse order, namely, first the unconditioned responses, then the strongest conditioned responses, and last, the weakest conditioned responses.

The order of reduction or loss of conditioned responses, however, was not constant. In one instance the responses passed through different stages in which all became equal or the weaker actually became greater than the stronger. In addition, the response to the weakest nonreenforced stimulus became slightly greater than that to the weakest reenforced stimulus.

The experiment in which the action of a large dose of sodium bromide was superimposed on a state of initial irregularity in the size of the response better illustrates the variations through which a response may pass before it is ultimately extinguished. Even before the sodium bromide was given, the light (the weakest reenforced stimulus) elicited practically the same response as the terminal ringing of the bell, a relatively strong stimulus, whereas the metronome beating 140 times per minute, a stimulus usually followed by no salivary response, was now followed by the secretion of an amount nearly equal to that elicited by either of the reenforced stimuli.

Similar effects of the narcotics ethyl carbamate (urethane) and chloral hydrate have been described (Lebedinsky [7]). The reaction most commonly observed was a gradual weakening of all the conditioned responses, the weak conditioned stimuli becoming ineffective before the strong ones. However, this sequence is not constant. The several variations described—those (1) in which weak and strong stimuli elicit equal response, (2) in which weak stimuli elicit larger responses than strong stimuli, (3) in which the nonreenforced stimuli elicit greater responses than the reenforced and (4) in which none of the other

7. Lebedinsky, quoted by Pavlov,[3] p. 278.

stimuli elicits responses—may readily pass from one into the other. The order is variable, and no deviation may be considered as a specific reaction to a given narcotic, nonreenforced stimulus or other threshold-raising agent (Pavlov [8]).

These irregularities are best considered as various expressions of the same progressive influence which any threshold-raising process of sufficient intensity may have on the different manifestations of the highest integrative functions.

It has been generally recognized that for varying periods following the administration of narcotics there may be a phase of increased activity which precedes the stage of depression. For example, in lower vertebrates "increased reflex excitability," as measured by the patellar jerk and respiratory activity and by increases in the shortening and force of contraction of the skeletal, cardiac and smooth muscles, is described as present during exposure to dilute solutions of various narcotics, whereas corresponding decreases are seen with more concentrated solutions (Winterstein [9]). The explanation of this observation is still wanting, but there is evidence suggesting that the variations described may be related to the concentration of drugs in the immediate neighborhood of individual cells. For instance, certain plants, protozoa and leukocytes, when exposed to dilute solutions of narcotics, show an acceleration in the flow of protoplasm and in growth, motility and ciliary movements, all of which are retarded in higher concentrations of the same substances (Winterstein [9]). Determinations of metabolism made on isolated tissue indicate a similar acceleration of biologic activity, although caution must be exercised in the interpretation of the observations. Thus, the oxygen consumption of timothy grass bacilli (Bacillus Phlei) is raised in the presence of 0.3 per cent ethyl carbamate (urethane) or five hundredth-molar to five thousandth-molar potassium cyanide, while it is lowered in more concentrated solutions (Loebel, Richardson and Shorr [10]).

The "recovery" and "postnarcotic" overresponsive phase in the dogs may be compared to the late effects of sodium iso-amylethyl barbiturate in man. After intravenous injection of from 0.3 to 0.9 Gm., or from 4 to 13 mg. per kilogram of body weight, cataleptic or stuporous patients pass through a period of about two minutes during which they talk relatively freely. Then they relax into a stuporous sleep. After this sleep has persisted for from four to eight hours the patients occasionally become more responsive than before the induced sleep. During the

8. Pavlov,[3] p. 280.

9. Winterstein, Hans: Die Narcose, ed. 2, Berlin, Julius Springer, 1926.

10. Loebel, R. O.; Richardson, H. B., and Shorr, E.: The Respiratory Metabolism of Acid-Fast Bacteria as Influenced by Foodstuffs, Narcotics and Methylene Blue, J. Clin. Investigation **11**:839, 1932.

latter period of several hours they may walk about, feed themselves and respond to questions and to many of the usual environmental stimuli (Bleckwenn [11]). Analogous effects have been observed during the action of other agents, notably carbon dioxide and sodium cyanide (Loevenhart [12]).

Another clinical phenomenon, possibly allied to that under discussion, is the fact that convulsions occur in some patients who discontinue phenobarbital or bromides after a prolonged and continuous use. These persons, who have been free from convulsions for months, may have, following the sudden withdrawal of the drug, a series of attacks which surpass in severity and number those experienced before the drug was administered.

It is improbable that the barbiturates in general or any individual members of the group are the only drugs that give this "double-peaked" curve of conditioned responses. It is not uncommon to find a prolonged period of underresponsiveness from any cause followed by a period of overresponsiveness (Pavlov [13]).

The action of small doses of sodium iso-amylethyl barbiturate, sodium bromide and chloral hydrate can best be considered together. The administration of small amounts caused only slight changes in the behavior of the animal when outside the chamber. Even within the chamber the effect was observed chiefly during the action of the nonreenforced stimuli, although some slowing in movement and a resting of the head and occasionally sleep occurred after the reenforced stimuli. The effect on the response to the nonreenforced stimuli was definite. Within from four to five seconds of the onset of the stimulus the dog was apparently deeply asleep and remained so during the full period between the stimuli. When the next reenforced stimulus sounded the animal immediately awoke, with the usual quick and brief orienting movements, which were followed by prompt conditioned movements and salivary response. There was an occasional delay in the onset of the conditioned movements and salivary response with a reduction in the volume of the salivary production, and the erect posture, quick movements and wakefulness were short-lived. After a minute or two the animal usually rested against the supports and seemingly slept.

Thus, even after small doses of the drugs the threshold became higher. This was particularly evident in the change of the response to

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11. Bleckwenn, W. J.: The Use of Sodium Amytal in Catatonia, in Schizophrenia (Dementia Praecox), A. Research Nerv. & Ment. Dis., Proc. **10**:224, 1931.

12. Loevenhart, A. S.; Lorenz, W. F.; Martin, H. G., and Malone, J. Y.: Stimulation of the Respiration by Sodium Cyanide and Its Clinical Application, Arch. Int. Med. **21**:109 (Jan.) 1918. Loevenhart, A. S.; Lorenz, W. F., and Waters, R. M.: Cerebral Stimulation, J. A. M. A. **92**:880 (March 16) 1929.

13. Pavlov,[3] p. 399.

the nonreenforced stimuli. Unlike caffeine sodiobenzoate, which dispelled sleep, these drugs seemed to facilitate its induction. The effect of the nonreenforced stimulus was augmented. The prompt relaxation and onset of sleep suggest that the effect on the threshold was diffuse, although the contrast between the responses to reenforced and those to nonreenforced stimuli was not reduced. In fact, with few exceptions the salivary responses to the reenforced stimuli after a small dose were well within the range of the control measurements and, on one occasion, were even greater than was usual.

The observations described in this report essentially agree with those made in Pavlov's laboratory.[14] A dog in which the responses had become irregular and weak was given 100 cc. of a 2 per cent solution of potassium bromide by rectum. At the end of ten days all the responses had returned to their usual and relative size. No reduction in the magnitude of the reenforced stimuli was observed as a result of the administration of the drug. In another of Pavlov's experiments the rectal administration of potassium bromide restored normal function in a dog in which irregular and weak responses had developed as the result of a difficult differentiation. In this dog the "strength of the positive conditioned action was not decreased but was even somewhat augmented" (Pavlov [15]).

The results of our experiments lend themselves to a slightly different interpretation. In the first place, it is clear that when bromide, chloral hydrate or sodium iso-amylethyl barbiturate is given in large doses it raises the threshold to both reenforced and nonreenforced stimuli. Only when the amount given is small or moderate is a degree of differential action noted. It is more in accordance with the observations to say that when small or moderate amounts of these drugs are administered the earliest effect is an increase in the influence of the nonreenforced stimuli. This is shown specifically not only in the complete absence of salivary responses when the nonreenforced stimulus is presented but more generally in the reduced motor activity, relaxation and sleep that follow these threshold-raising stimuli. The only perceptible effect on the responses to the reenforced stimuli is to delimit more strictly the influence of the latter to the salivary response and to hinder the extension of their threshold-lowering influence to the other functions. This curtailing effect is especially evident in the short-lived and decreased motor activity. To summarize, small or moderate amounts of these drugs, by raising the threshold of the highest integrative functions, accentuate first the effect of the threshold-raising stimuli. In addition they lessen the effect of the threshold-lowering stimuli.

14. Pavlov,[3] p. 300.

15. Pavlov,[5] p. 343.

THEORY

The Interaction of Threshold-Altering Processes.—The evidence presented justifies the inference that chemical substances which alter the threshold of the highest integrative functions are not essentially different in their effect from other threshold-altering processes. The interaction of the effects arising from drugs and conditioned stimuli does not permit precise mathematical expression, but rough measurements indicate that in combination the effects may be expressed as an algebraic summation.

The effect of a threshold-raising stimulus presented when the threshold is already raised owing to the administration of bromide is to add to the already high level, raising it still higher. Should the threshold be initially lowered owing to the action of caffeine, the effect of a threshold-lowering stimulus summates with the effect of the drug, depressing the threshold still further. Conversely, should the threshold be raised by the administration of bromide, the effect of a threshold-lowering stimulus would be reduced, and the amount of reduction would be dependent on the strength of its effect as compared to that of the bromide. In other words, a stimulus in altering the threshold does so on the basis of the already existent level and not alone by virtue of its inherent physical nature.

These considerations emphasize the futility of attempting to classify effects involving the highest integrative functions according to the origin of stimuli or the nature of the factors which produce these effects. Every stimulus, complex of stimuli, or in general every change in the internal and external environment of the organism affects the threshold for subsequent stimuli.

In other words, the conditioned response is the resultant of a multitude of factors which have their origin in the entire experience of the organism and not merely in the part of its experience directly connected with the conditioning stimulus.

These fundamental theoretical considerations should prove useful in the attempt to understand the reactions of animals with more complex integrative functions than those of the dog. They indicate the necessity of properly evaluating the many factors in the genesis of psychobiologic reactions.

SUMMARY AND CONCLUSIONS

1. The highest integrative functions were studied and quantitatively expressed in terms of one of the measurable components of the dog's "acquired" or "conditioned" responses to standard stimuli.

2. For the purposes of description the term "threshold-lowering stimulus" has been used to designate a stimulus which evokes a relatively strong response and which for a time increases the magnitude of the response to subsequent stimuli. The term "threshold-raising stimulus"

has been used to designate the stimulus which elicits little or no response and which for a time decreases the magnitude of the responses to subsequent stimuli. These terms are purely descriptive. They imply no knowledge of the anatomic or physiologic basis of the reactions they describe.

3. Caffeine sodiobenzoate lowers the threshold of the highest integrative functions. It accentuates the effect of the threshold-lowering stimuli and lessens the effect of the threshold-raising stimuli.

4. Small or moderate doses of sodium iso-amylethyl barbiturate, sodium bromide or chloral hydrate raise the threshold of the highest integrative functions. They accentuate primarily the effect of threshold-raising stimuli. In addition, they lessen the effect of threshold-lowering stimuli.

5. In larger doses the effect of sodium iso-amylethyl barbiturate may be divided into the following phases: (1) a brief phase during which conditioned responses are greater than the average, (2) the longer phase of narcosis, (3) the phase of recovery from narcosis and (4) (less constant) the postnarcotic phase during which the conditioned responses are again greater than during control periods.

Clinical Note

CALCIFIED INTRADURAL CHOLESTEATOMA OF UNUSUAL SIZE IN A PATIENT SHOWING MANIC-DEPRESSIVE SYMPTOMS

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Intracranial cholesteatomas of the type to which the name "pearly tumor" has often been applied comprise a distinctly rare group among tumors of the brain. Pathologic or clinical reports of these lesions are likely to find their way into medical literature for various reasons. In the epidermoid variety there is such a strikingly beautiful pearly luster that this, together with the rarity of such a growth, has often been deemed sufficient to warrant a report. From the year 1807, when Duméril [1] first described one of these tumors, there have appeared at intervals further individual and collective reports of cases of the condition, together with intensive discussions both as to the origin of the tumor and as to the nomenclature. Some of the more important and complete descriptions are those of Johannes Müller [2] in 1838, Virchow [3] in 1855, Bostroem [4] in 1897, Thomas [5] in 1901 and Bailey [6] in 1920.

Dermoid cholesteatomas were mentioned as early as 1745 by Verattus,[7] but those of the dermoid type are less likely to be classed as pearly tumors than are those of the epidermoid type because the covering includes more layers of the epiblastic tissue of origin and hence the shining luster of the contents may not be apparent. That this is not always true, however, was shown in one of Bostroem's cases and in one of the three which was reported by one of us (Horrax [8]) from the clinic of Harvey Cushing in 1922.

Read at the Sixtieth Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 5, 1934.

1. Duméril: Bull. Soc. facult. de méd., Feb. 19, 1807.

2. Müller, J.: Ueber den feineren Bau und die Formen der krankhaften Geschwülste, G. Reimer, Berlin, 1838.

3. Virchow, R.: Ueber Perlgeschwülste, Virchows Arch. f. path. Anat. **8:** 371, 1854.

4. Bostroem: Ueber die pialen Epidermoide, Dermoide und Lipome, und duralen Dermoide, Centralbl. f. allg. Path. u. path. Anat. **8:**1, 1897.

5. Thomas: Cholesteatomata of the Brain, J. M. Research **1:**220, 1901.

6. Bailey, Percival: Cruveilhier's "tumeurs perlées," Surg., Gynec. & Obst. **31:**390 (Oct.) 1920.

7. Verattus: De Bononiensi scientiarum et artium instituto atque academia commentarii, 1745, vol. 2, pt. 1, p. 184.

8. Horrax, Gilbert: A Consideration of the Dermal Versus the Epidermal Cholesteatomas Having Their Attachment in the Cerebral Envelopes, Arch. Neurol. & Psychiat. **8:**265 (Sept.) 1922.

Although most tumors of the general class under discussion are found within the dura, they may occur between the inner and the outer table of the skull. In this situation the slowly accumulating mass may attain great size and may markedly deform one of the cerebral hemispheres without giving any neurologic evidence of its presence. A notable example of such a growth was presented by Cushing [9] in 1922. In the case which he reported the tumor was roughly circular, measured 4 inches on two diameters (10 by 10 cm.) and weighed 175 Gm. The tumor was completely extirpated at operation. Because of absorption of bone in the skull a striking picture was shown by the roentgenogram (fig. 1), and it was predicted by Dr. Cushing that one would be able to make a diagnosis by this means.

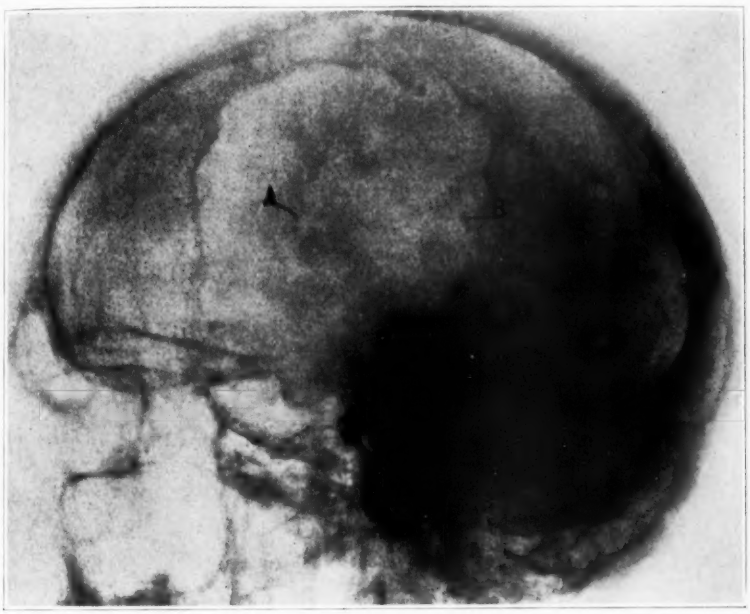

Fig. 1.—Roentgenogram of the skull of Cushing's [9] patient.

Shortly after the publication of Dr. Cushing's article, Dr. J. E. J. King of New York made what was, so far as we are aware, the first preoperative diagnosis of an exactly similar tumor by means of the roentgen findings. He reported the successful removal of the growth at a meeting of the New York Academy of Medicine on April 8, 1924. Dr. King has submitted for our inspection all the records, photographs and roentgenograms of his case and has allowed us to refer to it in the present article. The dimensions of the tumor in his case were 7 by 5 by 4 cm. (3 by 2 by 1½ inches), and although its weight was not given it must have been approximately that of the tumor which Dr. Cushing removed.

9. Cushing, Harvey: A Large Epidermal Cholesteatoma of the Parieto-Temporal Region Deforming the Left Hemisphere Without Cerebral Symptoms, Surg., Gynec. & Obst. **34**:557 (May) 1922.

namely, 175 Gm. It can be seen in figure 2 that the roentgenogram of the skull was practically identical with that of the skull of Dr. Cushing's patient.

The patient whose record forms the subject of our report showed a roentgenologic picture of the skull so similar to those of Cushing's and King's patients that it was thought before operation that we were dealing almost certainly with the same type of growth, although it could be seen by the roentgenograms that the mass lay completely within the cranium and not between the tables of the skull. The tumor was in fact a cholesteatoma, not only intracranial but entirely intradural, as will be seen in the sketch (fig. 6) made during operation and also by reference to the report on the operation. In addition, the tumor was surrounded by a thickly calcified shell.

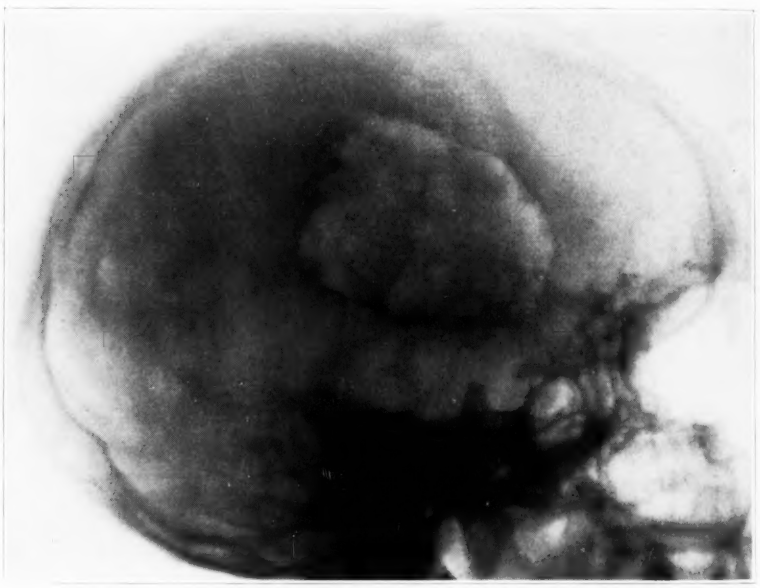

Fig. 2.—Roentgenogram of the skull of King's patient. Note that the appearance is almost identical with that shown in figure 1.

That a considerable indentation of either cerebral hemisphere may occur without evidence of mental or other neurologic abnormalities was evidenced by Cushing's and King's patients. Whether the marked mental symptoms in our patient were to be attributed to the presence of the enormous tumor is therefore debatable.

REPORT OF CASE

Calcified, intradural cholesteatoma, weighing 400 Gm. in a patient showing manic-depressive symptoms. Complete extirpation of tumor. Rapid and continuous improvement of mental symptoms after fifteen months.

History.—E. S., a woman aged 43, was admitted to the New England Deaconess Hospital on Dec. 9, 1932, by Dr. William A. Bryan and Dr. Morris Yorshis of the Worcester State Hospital. Her maternal great-grandmother had had

"epilepsy," and her maternal grandmother was described as "excitable and domineering." Her mother was nervous and excitable and had had two mental upsets in which she became seclusive. One sister had a "large head," and her condition had been diagnosed as dementia praecox.

The patient's birth was normal, at full term. She did not walk until she was 2 years of age. This was ascribed to excessive weight. She was said to have had a large head at birth. Her gait was peculiar from the first, and she often fell, striking her head. It was stated that as a child she had an "abscess on her head which required stitches." She was a good student in her earlier years. She completed high school and part of a year at college but was unable to keep up her grades, so she started to take a library course at another institution. This likewise she gave up, and several years later she tried to take a secretarial course elsewhere but could not continue. One summer she conducted a kindergarten school, and at other times she worked for short periods as a mother's helper and governess.

In 1908, at the age of 18, she had her first "nervous breakdown" about six months after attempting to continue in college. At this time she was "nervous, hysterical and depressed" and spent several months at a sanatorium. In 1918, at the age of 28, she had difficulty in various jobs she tried and began to act queerly. She was overactive, noisy and elated, dressed fantastically and showed a flight of ideas. In this year she was admitted to the Worcester State Hospital for the first time just after her sister had been committed to another hospital with a condition diagnosed as dementia praecox. During her stay the patient was untidy and foolishly elated and stated that she felt the effect of electricity at night and that many of the wires that ran through the hospital had an influence on her. She was discharged in 1920 with her condition diagnosed as manic-depressive psychosis, with recovery.

The patient was readmitted in February 1922, following the death of her father. She was violent, made irrelevant replies and once attempted to commit suicide. She was discharged in October 1925 with her condition diagnosed as manic-depressive psychosis (depressed). Until 1930 she was apparently adjusted fairly well, but was readmitted to the Worcester State Hospital in 1930 and was there until transferred to the New England Deaconess Hospital on Dec. 9, 1932, for operation.

Physical and Neurologic Examination.—Examination showed the patient to be an emotionally unstable woman, who walked about aimlessly, posing and exhibiting many mannerisms. She was elated and distractable, laughed and cried without cause and showed some flight of ideas. Judgment and insight were poor. Her head was large and of the hydrocephalic type, with prominent temporal regions, particularly on the left side. She had bilateral slight exophthalmos and a suggestion of facial weakness on the left. Examination of the fundi revealed some pallor of both optic disks. The fields of vision showed only slight general contraction, and visual acuity was 20/30 on each side. There was some deafness in the left ear as compared with the right, and occasionally she was found to have nystagmus on looking upward and to the right. The caloric responses were normal on both sides. Otherwise the cranial nerves were normal. The gait showed some slight unsteadiness, and the finger-to-nose test was rather poorly done with slight tremor. The abdominal reflexes were absent, and a positive Oppenheim's sign was present on the right side.

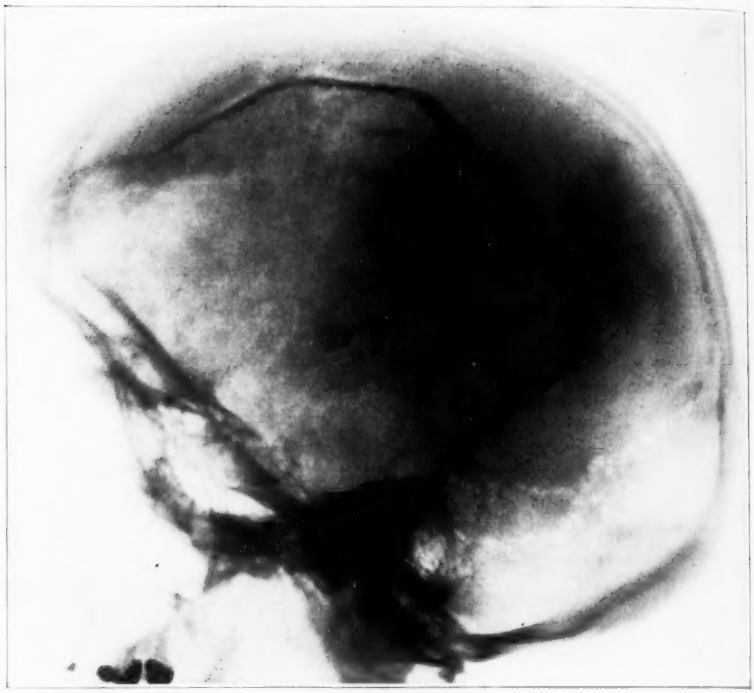

Fig. 3.—Left lateral roentgenogram of the skull of our patient (reduced one-half), showing the contour of growth. The outline is demarcated by a denser shadow than those seen in figures 1 and 2.

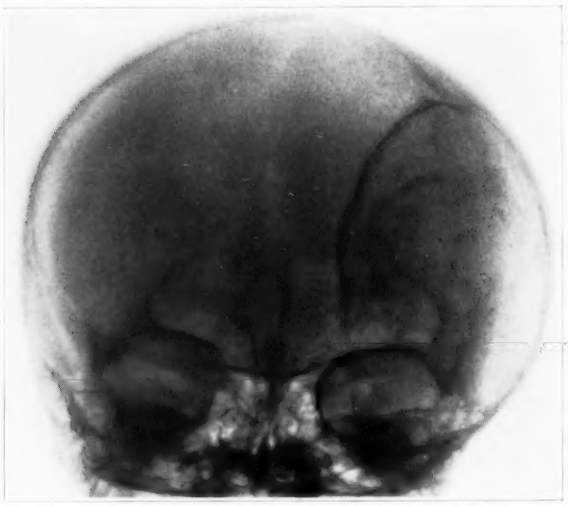

Fig. 4.—Anteroposterior roentgenogram of the skull of our patient. At the upper margin the outline of the tumor can be seen to lie distinctly inside the inner table of the skull.

Roentgenograms of the skull taken at the Worcester State Hospital showed the huge calcified shadow depicted in figures 3 and 4. It was because of this finding that Dr. Bryan referred the patient for surgical intervention. Reports on the roentgenograms by Dr. P. H. Cook of the Worcester State Hospital and Dr. M. C. Sosman of the Peter Bent Brigham Hospital were essentially the same. They described the skull as large and of hydrocephalic type, with no signs of increased intracranial pressure. The shadow was designated as being sharply outlined and filling a large portion of the left side of the cranium, with measurements of 15 cm. anteroposteriorly, 12.5 cm. vertically and 8 cm. in depth.

To those of the examiners who several years previously had seen the roentgenograms of Dr. Cushing's patient, the diagnosis of cholesteatoma appeared most logical. Other possibilities, however, were that the calcification might be surrounding an old subdural hematoma or an abscess. In order to gain an idea of

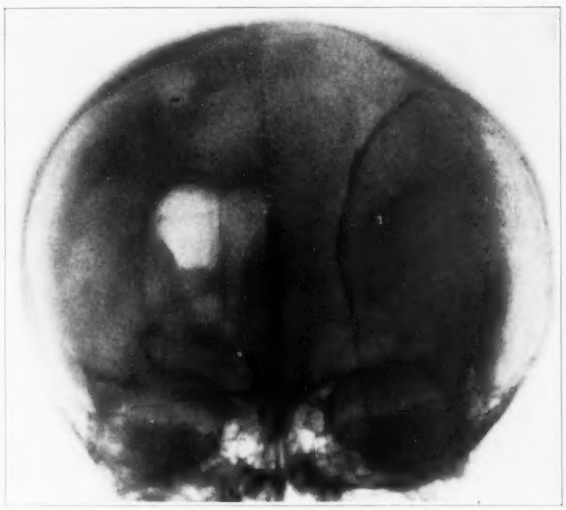

Fig. 5.—Ventriculogram of our patient showing both lateral ventricles pushed completely beyond the median line of the skull.

the degree of ventricular distortion by the tumor, a ventriculogram was carried out on Dec. 13. This showed that both ventricles were displaced beyond the median line (fig. 5).

First Stage Operation (Dr. Horrax).—Following the making of the ventriculogram, on the same day, with the patient under local anesthesia, a large bone flap was outlined over the left hemisphere. The dura was found to be extremely adherent to the under surface of the bone throughout the extent of the flap. Likewise, a large branch of the middle meningeal artery was encountered at the posterior portion of the field. All the bur holes were finally connected by Gigli saw cuts. So much time had been consumed in cutting through the bone that it was decided to remove the tumor at a second stage. The wound was therefore closed without drainage, the patient being in good condition throughout.

Second Stage Operation (Dr. Horrax).—On December 16, three days subsequently, the second stage operation was carried out with the patient under avertin

and ether anesthesia. The scalp wound was reopened, and an attempt was made to break up the bone flap in the usual way. The dura was so densely adherent to the bone, especially at the lower portion of the field in the temporal region, that it was deemed unwise to persist in this method. The scalp and the periosteum were therefore peeled away from the upper half of the flap, and this upper portion was then removed in two pieces and preserved in sterile gauze for reimplantation. The lower half of the flap was broken up after the densely adherent dura had been gradually scraped away.

It was now seen that the calcified mass lay entirely beneath the dura, extending forward to the frontal sinus and backward slightly beyond the posterior mar-

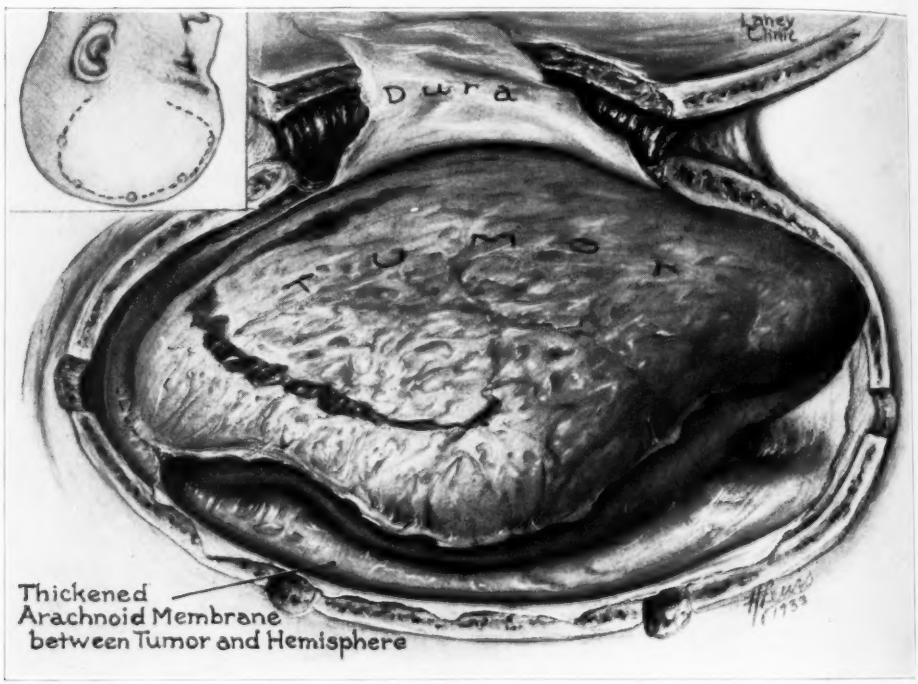

Fig. 6.—Sketch of the tumor made during the operation (about two-thirds natural size). The dura has been reflected from the surface of the tumor, and separation of the tumor from the underlying thickened arachnoid has been started.

gin of the bone flap. It also extended downward to fill up the temporal fossa, so that as much bone as possible was rongeured away over this region for a more complete exposure. The appearance was that of a bulging, resistant mass covered by dura and occupying the greater part of the left intracranial cavity. The dura was incised around the upper three quarters of the tumor, peeled away from the bony shell with some difficulty and reflected downward. This exposed the entire growth except that portion which extended down into and filled the temporal fossa, underlying bone in this area (fig. 6).

By lifting the upper margin it was possible gradually to scrape the tumor away from the ragged and somewhat thickened arachnoid to which it had become

attached. The greatly indented concave left hemisphere was apparent through this membrane and was not injured at any point. Finally it was possible to tilt the entire mass away from its moorings and lift it out intact except for a crack in the posterior end of the shell. In completing the enucleation the lateral sinus was torn at one point of adherence, but the tear was immediately controlled by placing over it a small piece of muscle.

At this point in the notes on the operation was this comment: "The appearance of the cavity was unique in my experience. The mass which had been removed represented almost a complete cast of the left hemisphere with the exception of the occipital portion, the temporal and frontal fossae having been entirely filled up and the left hemisphere as a whole pressed over to the median line of the head."

After all oozing points had been controlled the dura was resutured throughout to the incised margin, the two bone fragments representing the upper portion of the flap were fitted back into place, the lower part, of bone flap and scalp,

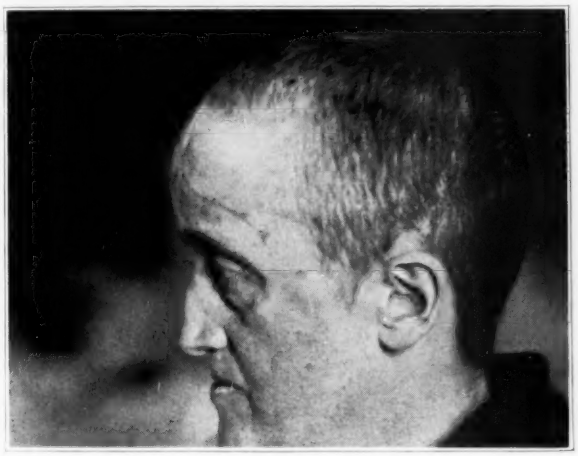

Fig. 7.—Lateral view of the patient at the time of discharge, showing the surgical scar.

was then brought back, and closure was made in layers with fine silk sutures without drainage.

Course.—The patient had a stormy night after the operation, but she improved within the next twenty-four hours and thereafter her immediate postoperative convalescence was relatively uneventful. The enormous cavity which had been left was tapped daily for a couple of weeks, after which the circulation of the fluid became readjusted and no further taps were necessary. Within three weeks she was up and about the ward, and on Jan. 19, 1933, she was taken back to the Worcester State Hospital. No great change had been noted up to this time in the mental condition, although it was thought that she talked less foolishly and was less flighty. Figure 7 is a photograph taken at the time of discharge and gives an idea of the operative scar.

On March 2, about two and a half months after the operation, her condition at the Worcester State Hospital was reported as follows: "She has shown

remarkable improvement mentally. She is much less facetious, seems to need less attention and is adjusting herself well."

Within another month she had become so well adjusted that she was discharged to her home. On May 19 she reported to Dr. Yorshis for an examination of progress. Her mental condition on that date was summarized as follows: "She was alert, considerably less facetious, behaved well and was quiet, in marked contrast to her usual overtalkativeness, silliness and distractibility. She apparently had very good insight in that she recalled that she used to be irritable, act foolishly and hear voices. All this behavior was absent." It was thought that the rapid progress which the patient had made was remarkable.

Fig. 8.—Photograph of the lateral aspect of the tumor (about two-thirds natural size).

She reported from time to time for further check-up, and at each examination a gradual improvement was noted. In December 1933, one year from the date of the operation, she volunteered to come to Boston to be presented at a local medical gathering. Her facetiousness, facial grimaces and flight of ideas had all disappeared. She was quiet, showed excellent insight and was well adjusted at home, where she had been living for eight months. No irritability, emotional instability or untidiness had been noted. There were few or no neurologic abnormalities except slight pallor of the right optic disk, some unsustained nystagmoid jerks and a liittle tremor of the right hand.

At the time of writing it is about fifteen months since the intracranial tumor was removed, and the mental progress has been marked and sustained.

Pathologic Anatomy.—The tumor was described by Dr. Shields Warren as an irregular, short-necked, gourd-shaped mass with dimensions 15 by 11 by 8 cm.

Fig. 9.—Photograph of the anteroposterior aspect of the tumor (about two-thirds natural size).

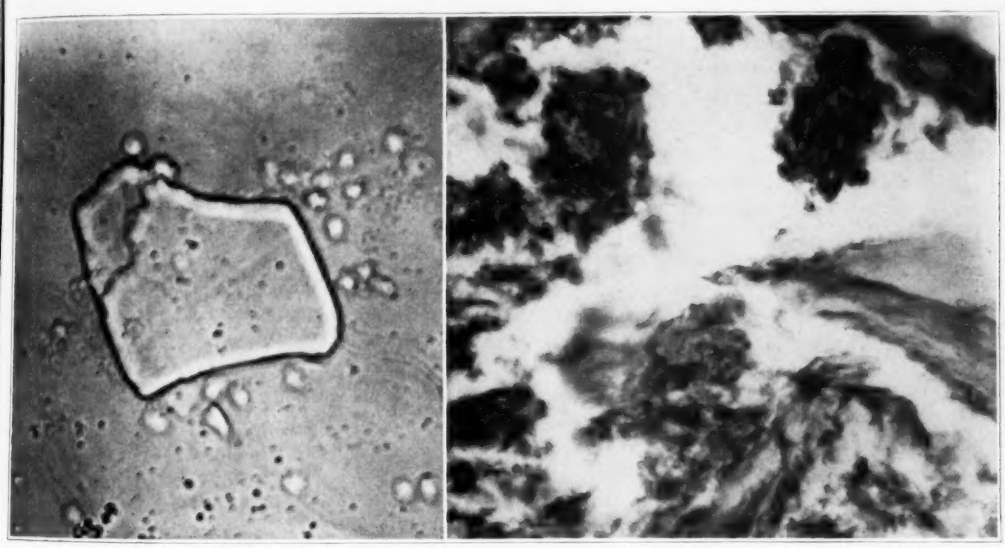

Fig. 10.—Photomicrograph of the contents of the tumor (× 120). At the left are seen cholesterol crystals; at the right, amorphous débris with lamination.

(figs. 8 and 9). It weighed 400 Gm. when received in the pathologic laboratory, but its true weight was possibly 15 or 20 Gm. in excess of this as some of the fluid and cheesy material were lost at the time the crack in the posterior part of the shell was made during the operation. Dr. Warren's note said further:

The surface of the tumor was completely calcified, the shell averaging about 1 mm. in thickness. The interior was filled with brownish-yellow, grossly amorphous material which was sticky and greasy, and glistening flecks of cholesterol were to be seen in this. Directly within the calcium shell was a lining from 2 to 3 mm. thick of yellowish, gelatinous material.

Microscopically, the material making up the contents of the tumor showed amorphous débris with some hint of lamination, granules of calcification and flat, sharply angulated crystals characteristic of cholesterol crystals. The latter were soluble in ether and were doubly refractive, which, with the morphologic characteristics identified them as cholesterol. Rarely a few compressed bodies were seen which were similar to the desquamated keratinized epithelial cells found in old dermoid cysts.

Microscopic Diagnosis.—The diagnosis was cholesteatoma (fig. 10).

COMMENT

It was pointed out briefly in the introduction of this paper that tumors of the type reported on here are commonly called either intracranial cholesteatomas or pearly tumors. Neither term is entirely correct, since some of the growths do not show the pearly luster and others do not contain cholesterol. For instance, the tumor in our case had no mother-of-pearl appearance for the simple reason that it was encased in a thick calcified shell. So far as we are aware no other example of such complete surrounding calcification has been reported for one of these tumors unless the calcified cyst mentioned by Craig and Kernohan [10] recently should be considered in this category. The content of the cyst in this case reported by Craig and Kernohan was a mass of cholesterol crystals, but the cyst was thought by the authors to have resulted from trauma. As Bailey [11] said, however, it makes no difference what terminology is employed, since tumors of this general class may be recognized unmistakably by their contents. In addition to the epithelial cells and keratohyaline granules there are likely to be "woody plant" cells, but whether hair, cartilage or other teratomatous material is present depends of course on the depth of the epiblastic inclusion. The important differential points to bear in mind about these tumors are that they are distinct from the cholesterol-containing cysts of Rathke's pouch and that they do not represent mere collections of epithelial débris which sometimes result from chronic otitis media. On the other hand, it should be said at once that the middle ear not infrequently may be the source of a true cholesteatoma or pearly tumor. A tumor which had attained the size of a hen's egg and eroded petrous bone down to the dura was removed successfully and described by Shefferd [12] in 1922. The tumor in the case we have just reported could not have had its origin in this site, however, because it lay wholly within the dura.

What, if any, was the relation of the tumor in our patient to her mental symptoms? There was some familial tendency to mental imbalance, and the patient had had several episodes of manic-depressive depression. For treatment

10. Craig, W. M., and Kernohan, J. W.: Cerebral Cysts, J. A. M. A. **102:** 5 (Jan. 6) 1934.

11. Bailey, Percival: Further Observations on Pearly Tumors, Arch. Surg. **8:**524 (March) 1924.

12. Shefferd, J. M.: Cholesteatoma of the Temporal Bone; with the Report of an Unusual Case, Boston M. & S. J. **186:**877 (June) 1922.

of these attacks she had been placed in the state institution, and after varying periods averaging from one to three years she had become adjusted sufficiently to be allowed to go home.

On the other hand the tumor had doubtless reached its large size many years before it was recognized, perhaps as early as the first mental upset, after which its wall had become calcified. We believe that the subsequent attacks which brought about admission to the state hospital did not in any way modify the organic changes which were taking place owing to the presence of the tumor. Whether she would have made a good adjustment to the situation at home if the growth could have been removed in 1908 is naturally debatable. Within a few months from the time the mass was removed she had become so well adjusted that she could leave the institution in which she had been confined for the previous three years, and up to fifteen months later she had shown gradual but continuous improvement. In fact, those of us (M. Y. and G. R. L.) who have been in frequent communication with the patient believe that she has become able to face intolerable situations much more evenly and with considerably better judgment than ever before, so that she no longer presents the residual evidence of a chronic manic state. She is sufficiently integrated, is not so boastful or talkative and exhibits better insight than any manic patient who was ever released from the Worcester State Hospital, whether treated by psychotherapy or not. The improvement came so promptly after the removal of the tumor and was so much more satisfactory and complete than was the case in her other remissions that we are led to hope that it may be permanent and may be attributed to the surgical therapy. In any event, it seems obvious that the tumor should have been removed on this assumption.

DISCUSSION

Dr. Percival Bailey, Chicago: This is a classic example, at least within the intracranial cavity, of a tumor developing from an embryonic rest. Such tumors vary from those which contain only epidermal cells to those which contain various dermal derivatives, such as glandular cells, sebaceous or sudoriferous, and even hair and teeth. So they vary from pure epidermoids, such as the tumor in this case, to those which contain various dermal derivatives and then, of course, through the teratoid tumors to the teratomas.

Purely epidermoid tumors, such as this one, which are usually called pearly tumors because of the shiny appearance of the etxernal capsule, are such as the surgeon would like always to find within the intracranial cavity because they are simply a mass of epidermal cells without any blood supply. They are very easy to remove and practically without bleeding. They may, as Dr. Horrax said, be found in any part of the intracranial or intraspinal cavity, from the scalp inward through the eye, the subarachnoid space, the intraspinal and intracranial cavities, and even within the substance of the brain or within the substance of the spinal cord, an intramedullary tumor lying within the dorsal septum of the spinal cord.

It is important when one operates on a tumor such as this to remove the growth in its entirety, because the only living, growing part of the lesion is on the outside and if one is not careful to remove that part the cells continue to grow and the tumor recurs, although it grows and recurs very slowly. It is not so important in the intracranial cavity because the tumor usually has plenty of room to expand, as in this case. In the spinal cavity, however, complete removal of the tumor is much more important because there the recurrence soon becomes obvious.

The roentgen picture of this type of tumor, particularly when it occurs in the diploe, is distinctive. It has a smooth, cleancut border, as in this case, and I have seen others with a dense border. I should like to point out that when these tumors lie within the diploe, they are apt to have an intracranial extension. On finding one at operation, one should be very careful to investigate the inner table carefully, and even though one finds only a hole the size of a pinpoint extending into the intracranial cavity, the intracranial cavity should be opened; usually there is also an intracranial extension outside the dura mater.

Dr. Joseph E. J. King, New York: The case which Dr. Horrax reported is most interesting and instructive. It is difficult to explain how a tumor could have reached the dimensions described by Dr. Horrax without producing not only paralysis, in the form of hemiplegia, but death. He showed splendid judgment in removing the lesion in two stages and great skill in effecting its complete removal, with recovery of the patient.

It is my belief that the lesion reached its maximum size some time ago, as stated by Dr. Horrax, and then became calcified, after which it was dormant and existed merely as a foreign body within the subdural space. It is difficult to classify this tumor. In the first place, it was intradural and not extradural as in Dr. Cushing's and in my two cases. It did not have the typical mother-of-pearl appearance on the surface usually presented by both extradural and intradural cholesteatoma, probably for the reason stated by Dr. Horrax, that the periphery of the lesion was calcified. It did not resemble the pearly tumors of Cruveilhier, so well described by Dr. Bailey in 1920 in his report of two cases. Bailey stated that these intradural growths are meningeal in origin and are not brain tumors proper. He stated that they "originate undoubtedly in the pial tissue beneath the arachnoid." Whether the tumor in the case reported by Dr. Horrax arose from the pia or not is likewise not known. I think it is believed by all, however, that these tumors are epithelial in origin and not endothelial.

I saw roentgenograms of the skull of a patient in 1923. These films showed a defect in the right frontoparietotemporal region so similar to that shown in the roentgenogram in the case reported by Dr. Cushing in the May 1922 number of *Surgery, Gynecology and Obstetrics* that I made the diagnosis of epidermal cholesteatoma from the films alone, without having seen the patient. The physical findings on examination of the skull were likewise similar to those in Dr. Cushing's case. I operated on this patient and removed an extradural cholesteatoma so similar in every respect to that of Cushing's patient that his description of the lesion and the findings at operation accurately described those in my case. This patient recovered promptly and is well. A report of this case was made at the meeting of the New York Academy of Medicine in May 1924.

Over a month ago, which was a short time after I received an invitation from Dr. Horrax to discuss his paper, roentgenograms of a patient were shown to me in Bellevue Hospital. From the films alone I was able to make a diagnosis of cholesteatoma. The patient was transferred to the neurologic service of Dr. Kennedy. The lesion was one of the posterior fossa and proved to be a typical epidermal extradural cholesteatoma. The only complaint was headache of a year's duration. I operated on the patient on May 1 of this year, verified the diagnosis and removed a tumor. He was discharged from the hospital on the twentieth postoperative day with relief of his headache and with no complaint.

With your permission I should like to show you slides of these two cases. The first slide shows the typical defect in the skull produced by an epidermal extradural cholesteatoma of diploic origin. In this instance the defect involved the frontotemporoparietal region of the right side. The slide is practically a duplicate

of the roentgenogram shown in Dr. Cushing's article in the May 1922 number of *Surgery, Gynecology and Obstetrics*. The only difference is that of size. The distinguishing characteristics are the scalloped border, the dense margin of the bony defect, and the thinned-out central area due to erosion or absorption of bone. This defect is in marked contrast to the feather-edged irregular or smooth margins of the defects produced by other types of erosive lesions of the skull.

The next slide represents roentgenograms of Dr. Cushing's patient and of mine for comparison. One can easily see the marked resemblance between the defects in the skull produced by the two lesions. Although I had not seen Dr. Cushing's paper in which he described this defect for over a year, the characteristics of the defect shown in the roentgenograms were so marked that I was able to make the diagnosis of epidermal cholesteatoma from the roentgenograms alone.

The next slide shows the anteroposterior view in which the two distinguishing characteristics are the sharp, dense line which indicates the margin of the defect and the markedly thinned-out area of skull external to this. The dark line is accentuated by superposition of the anterior and posterior margins of the defect, as if one were looking at a ring on edge.

The next slide shows three photographs of the cholesteatoma after removal. The upper photograph is of the external surface, showing the typical mother-of-pearl appearance. In one area the membranous lining of the lesion can be seen. The photograph below on the left shows the tumor placed edgewise, i. e., looking at the margin of the lesion. The mass measured 7 cm. in length, 5 cm. in width and 4 cm. in thickness and weighed about 120 Gm. The photograph below on the right is of the inner surface of the lesion, which is more irregular, less smooth and glistening and of a darker color. This surface was against the dura. The small fragment of bone shown alongside the lesion presents along one border the scalloped margin typical of the bony defect.

The material composing the mass was somewhat cheesy for the most part, but was covered on its external surface with a lamellated white substance. Typical cholesterol crystals were recovered. After the photographs were made the lesion was placed in a jar of solution of formaldehyde; it soon disintegrated and fell to pieces into a nondescript sediment at the bottom of the jar.

The next slide is a colored photograph of the lesion, which shows the beautiful luster of the external surface. At the left side a small area of the membranous capsule is still attached to the lesion. This capsule was exactly like that described by Dr. Cushing; it consisted of an outer zone of fibrous tissue, a middle zone of six or seven layers of polygonal epidermoid cells with normal staining reactions and an inner layer of lamellated desquamated epithelium.

The next slide shows a schematic drawing from Dr. Cushing's paper, representing a section of the tumor. This represents almost in duplicate the condition found in my case, the only difference being that of size. The mass shown compresses the dura and brain to an enormous degree, tending to push the structures around the midline to the opposite side, with flattening or obliteration of the lateral ventricle. It is difficult to understand how so much displacement of the brain itself could occur with so few neurologic signs or symptoms.

The next slide shows a roentgenogram of the skull after the operation. The slight bulging of the skull overlying the mass and the exact definition of the defect allowed accurate placing of the osteoplastic flap so that it was not necessary to make the usual large flap. Through this rather small flap the lesion was readily and completely extirpated.

The next three slides are photographs of the patient after the operation. He made an uneventful and complete recovery and is well today.

The next slide shows the roentgenogram of the patient in the second case. Although the tumor was situated in the left side of the posterior fossa, it presented the same typical markings as that in the first case, and, as in the first case, the diagnosis of epidermoid cholesteatoma was made without examination of the patient. Examination of the skull of the patient revealed the presence of two tumefied areas at the site of perforation of the skull by the lesion.

The lateral view of the skull shows the same typical margins throughout except in the anterior portion, where a part of the picture is obscured by the overlapping of the mastoid process, which contained cells. In the upper portion of the defect there is a distinct perforation of the skull by the lesion with a bridge of bone between it and another perforation below. The sharp, clearcut scalloped border seen in the other films is present. The lesion extended from the midline to the mastoid process and from above the lateral sinus to the posterior margin of the foramen magnum. It was covered with a somewhat grayish membrane which could readily be stripped away from the underlying mass. When this was done the typical pearly whiteness of the outer surface of the tumor was observed. On account of its position in the posterior fossa it was necessary to remove the tumor piecemeal. All of the membrane, however, was removed with the possible exception of some attached to the very thinned-out, markedly depressed dura overlying the left cerebellar lobe. As the mass was slowly removed, the dura gradually bulged up into view. This was in marked contrast to the depressed position of the dura maintained throughout the operation in the first case.

The next slide is a photograph of the patient seventeen days following the operation. He has remained well since.

A detailed report of these two cases of epidermal extradural cholesteatoma originating in the diploe will be published soon.

Dr. Byron Stookey, New York: These cases are interesting from the diagnostic standpoint. Those growing between the diploe showing changes in the bone with scalloping are very characteristic and can be diagnosed without other procedure. However, in the case that Dr. Horrax reported the tumor was inside the dura and showed calcification. I had two cases of an enormous tumor within the dura without calcification in the lining membrane and without scalloping. They were extremely difficult to diagnose. In one instance, the patient was operated on at Bellevue Hospital by my colleague Dr. Scarf and me two years ago. The patient was a policeman who had headaches about fourteen years without any other symptoms. This was an enormous right frontal tumor which we were able to take out in toto, together with the lining membrane. That and the one I removed in 1924 or 1925 at the Neurological Institute were enormous, were within the dura and had practically replaced the entire frontal and temporal lobes. In the second case I did the operation in two stages. In the first stage the dura was so tense that I could not get any reduction in the tension by the injection of dextrose intravenously, so I deferred the operation. The patient returned, and I opened the dura, inserted a needle in the brain and aspirated clear fluid. This was done, however, at the first operation, and the fluid was so clear that I thought it was ventricular fluid. In the second stage, the fluid showed some rather floccular material and a somewhat milky appearance, something like that of coconut milk. On examination typical crystals were found, and I proceeded with the operation.

In both instances there was recovery, and both patients are now doing very well. The diagnosis in the case of the policeman was made by the encephalogram and the diagnosis in the other case, because of involvement of the temporal lobe, by studies of the visual field. I think this type of tumor offers no great problem

to the surgeon once the diagnosis is established, but the recognition of the condition is extremely difficult without the aid of special studies, as with the ventriculogram.

DR. ADOLF MEYER, Baltimore: As this paper is evidently placed in this forenoon session as having a bearing on the respective relations of neurology and psychiatry, I should like to say a word with regard to the statement that was made that there seems to be no doubt that the patient has recovered or is on the way to recovery from a chronic manic-depressive condition. It is dangerous to speak of manic-depressive conditions as chronic. After all, the tumor was evidently remarkably well encapsulated and had only a displacing influence on the brain. On the other hand, one deals with a patient or personality that has in the hereditary make-up the material for deviations of the type of manic-depressive reaction. For example, I could tell of a patient from the Worcester Hospital who had for four years a closed cycle of supposedly chronic manic-depressive type; then, through the extraction, or rather the surrender on her part, of a story instead of a tumor, she made an adjustment which put at any rate a temporary stop to the manic-depressive condition. There is a certain amount of mutual illumination of the conditions that deserve mention.

It is obvious that because of this tumor the brain did suffer, but not to such an extent that the source of the suffering did not leave to the original structure of the personality its way and its expression.

I like to remind my colleagues of the fact that in the study of manic-depressive psychoses one has to take many things into account. The case on which most of the intensive work was done by Hoch and Folin, a case described as one of manic-depressive psychosis, proved to be one of dementia paralytica. Even through internal destruction and disorders one can get manic-depressive pictures. In the case report here there was a manic-depressive constitution, to judge by the family background; perhaps by giving the brain a chance, the personality of the patient also has a better chance.

DR. ALFRED GORDON, Philadelphia: A few days ago at the meeting of the American Psychiatric Association, I spoke of combined psychoses and cited among other cases one in which the patient had a typical symptomatology of dementia paralytica, with motor and mental phenomena, typical changes in the cerebrospinal fluid and other symptoms. It was a genuine case. During the remission which followed the course of very intensive treatment the patient gradually began to show mental phenomena totally different from those of dementia paralytica. The manifestations reminded one very much of dementia praecox. The question arose: What is the connection between one and the other? In this paper, the tumor in the brain might be a point of help to those of the members—of neurologists and psychiatrists—who claim that pathologic conditions in the brain (when I say pathologic conditions, I mean histologic conditions) are capable of bringing on mental symptoms and psychoses. Particularly may I mention the opinion of Baruk, of France, who has written so much on the subject. The question comes up whether pathologic lesions per se are capable of bringing on typical psychoses such as those presented here.

My personal investigation of that problem has been going on for several years and makes me doubt whether a cerebral pathologic lesion is capable of causing a psychosis. It is the personality make-up which Dr. Meyer insisted on that has to be taken into consideration.

From the cases reported here and from other facts presented today, I feel that the pathologic lesion is a sort of *primum movens*, or an exciting factor, to split the

personality and bring to the surface those peculiarities and characteristics of the personality which have been hidden.

In the case of Dr. Horrax, he distinctly mentioned that the family history and the hereditary features were conspicuous, but nothing is known about the personality characteristics of the patient before the pathologic symptoms developed. I doubt whether the brain tumor could be considered causative; it was simply a point of departure, a start, a flare-up, of conditions which existed a long time in this patient.

Dr. Gilbert Horrax: I knew I was treading on dangerous ground to suggest that this might be associated with a manic-depressive psychosis, but I hoped it would bring forth just such a discussion as it has, and I am appreciative of the discussion and of the light shed by Dr. Meyer and by the others who have taken part in the discussion.

AN APPARATUS FOR THE SIMULTANEOUS DISPLACEMENT OF SPINAL FLUID AND THE INJECTION OF AIR FOR ENCEPHALOGRAPHY

HARRY D. PIERCY, M.D., CLEVELAND

Liberson [1] and others [2] have called attention to the importance of maintaining the intracranial pressure at a point as near constant as possible during encephalography. This is best accomplished by using a "closed system" which, in its simplest form, consists of a bottle with tight fittings, the contained air being displaced into the subarachnoid space by the inflowing spinal fluid.

A number of designs of apparatus for the simultaneous exchange of spinal fluid and air exist. All effect this exchange without causing repeated and violent fluctuations in the intracranial pressure. However, two important considerations are not adequately controlled in these instruments: 1. No provision is made to give visible evidence at all times of the tightness on the "air" side of the apparatus. 2. No means have been suggested for balancing the pressure within the bottle against the pressure of the cerebrospinal fluid at the start of the procedure. These considerations are of vital importance if the minimal disturbance of intracranial cerebrospinal pressure is to be obtained and if the amount of fluid withdrawn is to represent accurately the amount of air injected into the subarachnoid space.

To control these factors the instrument herein described was designed and constructed.[3] The accompanying illustration shows clearly its construction and manner of use. A bottle of 200 cc. capacity is held in a phosphor bronze clip which permits ready insertion and removal. The design of the base and the box protecting the manometer provide for a firm and easy grip on the whole apparatus. The U-type mercury manometer is attached to the hinged cover of the box, which when closed affords secure protection to that delicate instrument. The bottle is provided with a rubber stopper through which pass three tubes. One is connected with the manometer, and the other two provide for the intake of spinal fluid and for the escape of the displaced air, respectively. A one way stopcock is attached to the "fluid" side, and a three way stopcock is mounted on the "air" side. The whole apparatus is fastened to a bakelite base.

The essential feature of the apparatus is the attachment of the manometer to the bottle in the manner described. As this is a closed system, the bottle, by virtue of its two way connection with the subarachnoid space, has become an extension chamber continuous with that space; pressures in both chambers and

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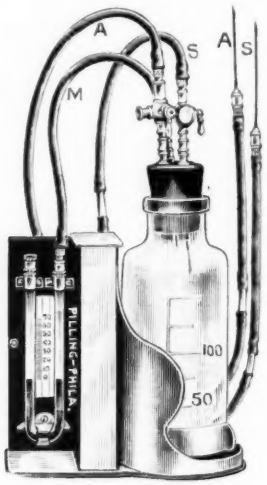
1. Liberson, F.: Apparatus for Simultaneous Displacement: Designed for the Simultaneous Displacement of Fluids in the Spine, Joints or Body Cavities, by Air or Other Gas, Arch. Neurol. & Psychiat. **12**:300 (Sept.) 1924.

2. Sommer, F. C.: A New Apparatus for Replacement of Cerebrospinal Fluid by Air in Encephalography and Ventriculography, Arch. Neurol. & Psychiat. **26**:1337 (Dec.) 1931. Waggoner, R. W., and Clark, D. M.: New Position Used in Encephalography, Am. J. Roentgenol. **25**:533 (April) 1931.

3. This apparatus is made by the George P. Pilling & Son Company, Philadelphia.

in the tubes are quickly equalized, and, in the absence of leaks, tend to be constant. The manometer thus serves to register the cerebrospinal fluid pressure. Its principal use, however, is to furnish evidence of the tightness of the "air" side of the apparatus. It is obvious that a leak anywhere in the apparatus would result in registering a fall in cerebrospinal fluid pressure. A leak on the "fluid" side is readily apparent, but a leak on the "air" side can be detected only by the use of such indirect means. A rapid or even a gradual fall in the mercury column is likely to indicate a loss of either fluid or air. Without the means of recognizing this loss as provided in this apparatus the operator cannot be aware that a loss has occurred and may be both surprised and chagrined to find that he has succeeded in injecting little air into the fluid spaces of the cranium. The manometer serves as a constant check on the integrity of the whole closed system.

The attachment of the three way stopcock on the "air" side of the apparatus offers special advantages in making adjustments of the pressure within the system.



Apparatus for the simultaneous displacement of spinal fluid and the injection of air for encephalography.

Its principal use, however, is to afford the operator a means by which he may balance the pressure in the bottle against that of the cerebrospinal fluid. This is of great practical importance. If the pressure in the bottle is lower than the cerebrospinal fluid pressure, spinal fluid flows down both tubes, and no exchange of air is possible until the inflowing fluid has raised the pressure in the bottle so that it equals the now greatly reduced cerebrospinal fluid pressure. Unless the pressure is adjusted in this manner at the start of the procedure, a marked fall of cerebrospinal fluid pressure and a loss in volume of air injected is inevitable. The valve also has the advantage of enabling the operator to inject air directly into the subarachnoid space.

The manner in which the apparatus is used is as follows: The bottle, stopper, all connecting tubes and a rubber bulb or a 20 cc. syringe with Luer fittings are sterilized. The bottle and its connections are properly assembled; the tube leading to the manometer is firmly seated in one arm of the latter, and the stopcocks are turned off. The arm of the three way valve is turned to the left, which

places it in the proper position for the adjustment of the pressure in the bottle. The rubber bulb or the syringe is attached to the side adapter of the three way valve. The patient, under the influence of from 6 to 9 grains (0.4 to 0.6 Gm.) of sodium amytal, or an equivalent dose of some other barbital preparation, is placed in the conventional sitting position, and two lumbar puncture needles are inserted into the subarachnoid space. The "fluid" tube is then attached to the lower needle and the "air" tube to the upper needle. With the rubber bulb the pressure in the bottle is raised to 20 or 30 mm. of mercury. The stopcock controlling the inflow of fluid is turned on, and fluid is allowed to run slowly down this tube until it just passes the window 10 or 12 cm. from the needle. At this point the pressure in the bottle is raised sufficiently to push back the head of the column of fluid to the midportion of the window and to hold it there. The handle of the stopcock is then turned downward, thus establishing the air connection between the bottle and the subarachnoid space. The fluid immediately starts to flow into the bottle, while the air simultaneously rises into the subarachnoid space. By this maneuver the pressure in the bottle is just balanced against the cerebrospinal fluid pressure, and the displacement of fluid by air is initiated with a minimal disturbance of intracranial pressure. A reading of the manometer is taken at the start of the procedure, and any sign of a fall in pressure is followed by a checking up of all the joints for tightness.

As one works with this method for encephalography one is impressed with the fact that the "closed system" is sound both in theory and in practice. The old method of alternately withdrawing fluid and injecting air gives rise to great fluctuations in cerebrospinal fluid pressure. Careful consideration of the two methods leads to the conclusion that the "closed system" best meets the physiologic conditions with which one must deal and, in addition, possesses the following advantages: 1. The operation is conducted with greater ease and neatness. 2. The amount of fluid withdrawn and that of air injected are accurately determined. 3. The reaction of the patient is definitely less violent. In 1933 Liberson [4] reported two hundred and ten cases in which the "closed system" was used. Among these there were eight cases of tumor of the posterior fossa (a condition which has been considered a contraindication for encephalography), and not a single fatality occurred.

This apparatus has been in use for over one year. The advantages claimed for the peculiar details of its construction and for its modus operandi have been demonstrated in every case in which it has been employed.

10515 Carnegie Avenue.

4. Liberson, F.: Use of Various Gases in Encephalography, Am. J. M. Sc. **185**:478 (April) 1933.

PERIODIC ATTACKS OF GASTRIC PAIN ACCOMPANIED WITH MARKED CHANGES IN ELECTRICAL RESISTANCE OF THE SKIN

MAURICE LEVINE, M.D., AND CURT P. RICHTER, PH.D., BALTIMORE

The case to be reported is of interest not only because of the periodicity of the attacks but because of the marked changes in the electrical resistance of the skin which accompanied them.

REPORT OF A CASE

In 1931 Mr. S., aged 31, was admitted to the Henry Phipps Psychiatric Clinic complaining of periodic attacks of severe abdominal pain. The attacks, which were localized over the lower ribs on the left side, lasted for from three to thirty hours and recurred at intervals of from eight to twelve days. They were often associated with vomiting and headache and usually incapacitated the patient for work. The only possible explanation of their onset lies in the fact that at about 4 years of age the patient suffered severe trauma in the gastric region when he fell from a tree and landed on a rock. The attacks started when he was between 5 and 6 years of age and occurred with fair regularity thereafter, no relief being obtained from an appendectomy at the age of 12.

Five attacks observed in the Phipps Clinic varied in duration from three to twenty-five hours and were separated by intervals of from five to ten days. They were preceded by periods of depression, listlessness, lack of interest and marked salivation. During the attacks the patient moaned and cried and afterward was very tired.

Physical examination revealed no local defects or disturbances which accounted for the attacks, except spasticity and irregularity of contraction in the region of the pylorus as shown roentgenographically. Other standard tests gave negative results. The patient persistently swallowed air. He appeared to be in good health, with no abnormality except a tendency to vagotonia, as indicated by constricted pupils, slow pulse and an oculocardiac reflex so marked that in one instance the heart stopped beating for nineteen seconds.

A study of the personality disclosed that the patient had had a nagging mother, had run away from home on two occasions and had been unhappy most of his life except for a short period immediately after marriage at the age of 28. The two years preceding his admission to the Phipps Clinic were particularly unpleasant, however, because of difficulty and misunderstanding with his mother-in-law. The attacks had been much less severe and less frequent during the short interval after marriage, but subsequently they had become worse than before.

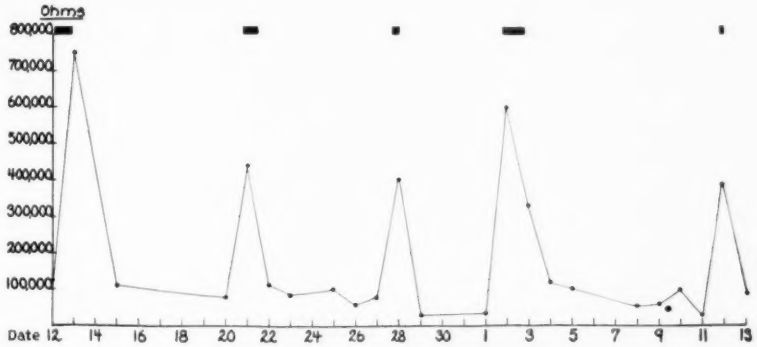
In examinations made during the attacks it was found that the most constant and marked change was in the electrical resistance of the skin, as measured by the string galvanometer with kaolin-zinc electrodes attached to the palmar surfaces.

From the Psychobiological Laboratory, Henry Phipps Psychiatric Clinic, Johns Hopkins Hospital.

In the accompanying chart in which the results are graphically presented, the resistance expressed in ohms is indicated on the ordinates and the time in days on the abscissas, and the occurrence and duration of the attacks are properly noted. It can be seen that simultaneously with the attacks there occurred a great increase in the electrical resistance of the palmar surface of the skin, from an average value between the attacks of less than 75,000 ohms to a value in one instance of over 750,000 ohms. It will also be noted that the magnitude of the increase in resistance was roughly proportional to the duration of the attack.

COMMENT

The appearance of an increase in the electrical resistance of the skin during the attacks of pain is of particular interest, because pain ordinarily produces a marked decrease in resistance. The significance of the increase during the attacks is not clear. It is known that similar large increases take place in normal and pathologic sleep and after sympathectomy (Richter [1]). The patient whose case is reported here did become drowsy during the attack but, because of the intense



Relation of electrical resistance of the skin of the palmar surfaces to attacks of gastric pain. The solid rectangles indicate the duration of the attacks.

pain, was unable to sleep. That the change in the resistance of the skin may indicate a decrease or cessation of activity of the sympathetic nervous system is consistent with the constricted pupils, slowed pulse, oculocardiac reflex and increased salivation. However, these vagotonic features were present between the attacks and were not exaggerated by them, whereas the resistance of the skin was increased only during paroxysms. That there is a close relationship between disturbances in the sympathetic system and pain is well known, and one of us has had occasion to observe severe attacks of pain in a patient in whom the sympathetic chain was apparently blocked on one side by a tumor (Richter [2]).

In the present case the five attacks observed in the clinic had a doubtful periodicity. However, the fact that such attacks had recurred for years before at intervals of approximately ten days seems to point definitely to a periodic response.

1. Richter, C. P.: The Significance of Changes in the Electrical Resistance of the Body During Sleep, Proc. Nat. Acad. Sc. **12**:214 (March) 1926.

2. Richter, C. P.: A Study of the Electrical Skin Resistance and the Psychogalvanic Reflex in a Case of Unilateral Sweating, Brain **50**:216, 1927.

If it were possible to locate an organ within the body with a similar ten day cycle, definite advance would be made toward a solution of the etiology of the condition. At the present time, however, no organ is known which possesses such a rhythm, although a four to six day cycle in sleep is recognized which may be related to disturbances of the pituitary gland (Richter,[3] 1934).

The attacks may be viewed as manifestations of migraine, as headache appeared as a frequent, although not a constant, accompaniment, but they may better be considered as a part of profound changes in the entire autonomic nervous system.

3. Richter, C. P.: Cyclic Manifestations in the Sleep Curves of Psychotic Patients, Arch. Neurol. & Psychiat. **31**:149 (Jan.) 1934.

A WORD OF CRITICISM ON THE DESIGNATION "LOCALIZATION OF FUNCTION IN THE CEREBRAL CORTEX"

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Two years ago a symposium on cortical localization was held by the Association for Research in Nervous and Mental Disease. The collected papers of that symposium have recently been published under the title "Localization of Function in the Cerebral Cortex." I know that this term is commonly used, though it is certainly open to objection and, in my opinion, is fundamentally incorrect.

An enormous number of nervous activities involve not only the cortex but also other levels of the nervous system. This is true of the human being, so far as is known, for all perceptual and voluntary activity. This means, irrespective of one's point of view in regard to the problem of functional localization within the cortex, that it is incorrect to state that vision, hearing or motility is "localized" in the cerebral cortex. If this term is used, the only appropriate statement would be that the nervous function under consideration is "localized" in all those nervous structures which are thrown into activity in the performance of the function.

Whether there are nervous activities which occur in the cortex exclusively, without any participation of or reverberation on lower levels, is an open question. Even if such nervous activities exist, it is again an open question whether the principle of functional localization witnin the cortex holds true for them. Be this as it may, this problem is irrelevant here.

The point is that an enormous number of nervous activities in which the cortex participates are said to be localized there, notwithstanding the fact that they actually involve concomitant activities of other levels of the nervous system. This stamps the term "localization of function" in the cerebral cortex as erroneous.

The original manuscript of my paper in that symposium contained a short paragraph to this effect. I omitted that paragraph from the final manuscript read before the Association. It was withheld because I thought that my remarks might be looked on as self-evident and interpreted as sophistry. From the title chosen for the collected papers of that symposium it is clear that my reflection was wrong, and I regret now that I suppressed those remarks.

The purpose of this note is to stress that the term "localization of function in the cerebral cortex" is wrong, and to advocate the use of the correct designation already existing for one of the most fascinating problems in neurology, that of "functional localization in the cerebral cortex."

From the Laboratory of Neurophysiology, Yale University.

SPECIAL ARTICLES

IVAN PETROVITCH PAVLOV
1849—

GEORGE W. STAVRAKY, M.D.
MONTREAL, CANADA

When one considers the most outstanding scientists of modern time Pavlov's name is among the first to enter one's mind. Men like Pavlov may occasionally be born in any country, come from any class of society and yet be so independent in judgment, so original in thought, that they develop into international figures and command universal admiration for centuries. Such exceptional personalities require certain conditions for their development, not the least of which is liberty—liberty to choose a field of work, liberty to develop original interests and liberty to estimate the value of their own achievements.

These traditions of freedom in Russian science have been firmly established by such towering personalities as Lomonosov, Lobacherski, Pirogov, Mendeleeff, Schenov and many others. Russian science was flourishing at the time of Pavlov's student days, and in retrospect it is easy to see how it happened that he was carried away by the thrill of research and later devoted his whole life to science.

Born on Sept. 26, 1849, in the modest city of Riazan, Ivan Petrovitch Pavlov came of a family of poor country priests. In childhood he enjoyed almost unrestrained freedom. Being left-handed and not very strong, but eager and ardent, the boy, with a persistence remarkable for his age, trained himself by constant exercise and developed muscular power enabling him to rival in games boys of his own age.

He studied grammar at 7, but began his real education at the age of 11 in the church school and continued it later in the theological seminary. Often in later life Pavlov remembered the seminary with affection and pointed out that, in contrast to the classical schools of his

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The material for this biographical sketch was derived from personal acquaintance and from association with Pavlov's closest co-workers and pupils, such as B. P. Babkin, L. A. Andreyev, P. S. Koupalov and S. A. Komarov, as well as from the biographies of Pavlov by: R. Tigerstedt (Arch. d. Sc. biol. **11**:1, 1904); W. W. Savitch (Pavlov's Seventy-Fifth Anniversary Volume, Moscow, 1924, p. 3); W. H. Gantt (I. P. Pavlov's Lectures on Conditioned Reflexes, New York, International Publishers, 1928, p. 11); B. P. Babkin (Russkaia misl. **9-12**: 306, 1923-1924); B. P. Babkin (Canadian M. A. J. **21**:582, 1929, and Klin. Wchnschr. **8**:2030, 1929), and others.

time, there was in the seminary no tendency to require equal marks in all subjects, and if a boy showed interest and ability in one field the teachers were apt to overlook his neglect of others.

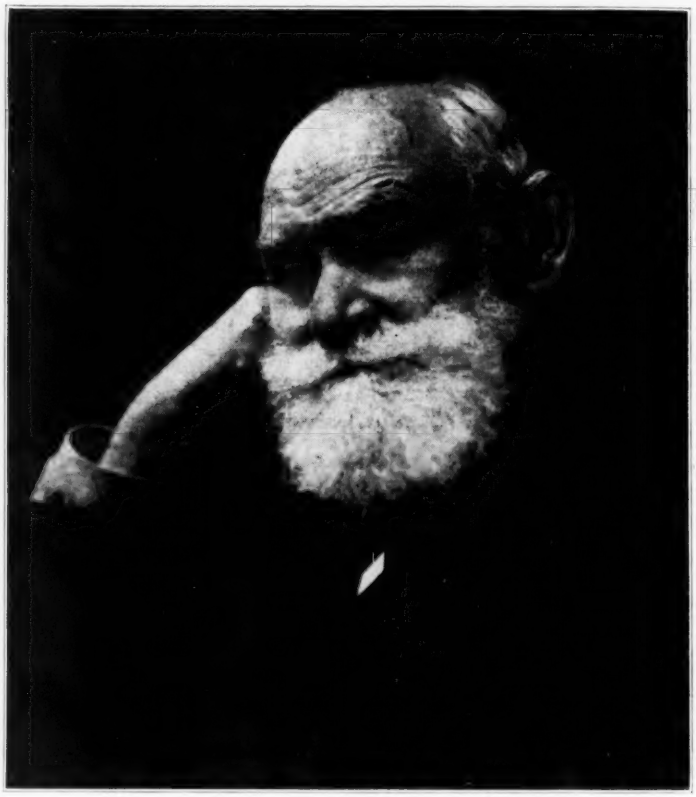
Having become interested in the natural sciences, Pavlov in 1870 left the theological seminary and entered St. Petersburg University, where he studied under such famous teachers as Mendeleev and Butlerov. Later he joined the Medico-Chirurgical Academy, from which he graduated in 1879. In the Academy he was greatly influenced by the brilliant physiologist, Prof. E. von Cyon, and it was this influence of Cyon and the fame of Sechenov that determined his future career. After graduation Pavlov continued his physiologic studies and research, working in the capacity of *chef de laboratoire* in the Clinic of Internal Medicine at the Military Medical Academy under Prof. S. P. Botkin. During this period he discovered, independently of Gaskell, the dynamic nerves of the heart.

In 1884 he was awarded the Wylie Fellowship, and he spent two years abroad, completing his training under C. Ludwig in Leipzig and R. Heidenhain in Breslau. On returning to his former position in 1886, his interests were concentrated on the physiology of digestion. In 1888 came his discovery of the secretory nerves of the pancreas—a discovery which for twenty years remained unconfirmed, so difficult was the experimental technic! The following year he described the famous experiments with sham feeding. Dissatisfied with the crudeness of the conditions in "acute" experiments and impressed by the progress of aseptic surgery, Pavlov applied the latter to physiology, developing the principle of "chronic" experiments, and in consequence of this new technic made rapid progress in the understanding of digestion. In 1897 he published his classic monograph on the work of the digestive glands, which has been translated into many foreign languages and which placed him among the world's leading physiologists.

In spite of his remarkable advances in research he was not successful in the early period of his career and only in 1890 obtained an independent position as professor of pharmacology in the St. Petersburg Medical Academy. A year later he was appointed also director of the department of physiology of the newly built Institute of Experimental Medicine. In 1895 he gave up his position as professor of pharmacology and obtained the chair of physiology in the Medico-Chirurgical Academy, which he retained till 1924. These two positions gave him the desired facilities for his work, removed all pecuniary difficulties and aided much in the full development of his exceptional experimental talent.

In 1902, when he was seemingly at the peak of his fame, came the discovery of secretin by Bayliss and Starling. Pavlov's laboratories were among the first to confirm it. But the theory of humoral correla-

tions was a severe blow to Pavlov. All his life he had concentrated on nerves, assuming a priori only nervous correlations, and now many facts appeared in a new light and he had to discard many of his explanations. He did this as unflinchingly as only a truly great man could. From the start he realized the importance of this new discovery and clearly foresaw that further advances in the physiology of digestion would have to follow chemical lines with which he had little familiarity.



IVAN PETROVITCH PAVLOV
1849—

This severe disappointment apparently turned his interest away from digestion, and 1904, besides bringing him the Nobel Prize in medicine, saw the fruition of a new idea, by far the most brilliant of all—that of a method by means of which he might be able to prove that the activity of the brain is based on a principle of reflex action not unlike that of the spinal cord and nervous system of lower organisms. With his usual energy, enthusiasm and persistence he set to work in this

new field, and for thirty long years conditioned reflexes have held his attention. Much patience, much ingenuity and hard work were involved, and gradually a new, classic and as yet unlimited chapter in the physiology of the nervous system was revealed.

As may be observed even from this brief sketch, the fields of Pavlov's activity are manifold. Circulation, digestion and the reflex activity of the cerebral hemispheres stand widely apart. But there is one feature common to all his work—its integrating tendency. If Claude Bernard was the first to emphasize the importance of the so-called "integral" (I. de Burgh Daly) or "synthetic" (Babkin) physiology, in contrast to "analytic" physiology, no one has contributed more to it than Pavlov. His great interest in the correlation of the various functions of different organs in one harmonious process of life explains well the prominent part that the study of nervous influences plays in every field of Pavlov's work. If there is any justification for the subdivision of physiology into different branches, such as neurophysiology, cardiology and endocrinology, Pavlov may be said to be equally prominent in several of them and probably achieved most in the field of neurophysiology.

Different emotions and causes drive men to activity; among these are necessity, anguish, vanity, pride, a spirit of gambling, an earnest desire to live up to one's position or ideal and the attempt to escape from reality in work. Profound curiosity, the joy of achievement and an infinite love of truth are perhaps some of the most prominent impulses underlying Pavlov's activity. Considerations of a career never enter his work. He loves physiology; science is sacred to him. He placed his whole life on the altar of his idol, and the grateful goddess in return revealed to him many of her vital secrets.

As so ably translated by Gantt, Tigerstedt said of Pavlov in 1904: "Pavlov's life can be summed up in this: an untiring search for truth has led him to the attainment of scientific facts of the first order." How much more significant this brilliant characterization appears in 1935.

On looking back at all that Pavlov has achieved, one question is frequently asked: How did he do it? The secret of scientific success undoubtedly lies in the man himself. Even if the conditions for a certain discovery are already prepared, the realization needs perfect judgment and complete education, besides the energy, insight and independence of thought necessary to carry a scientific adventurer through all the difficulties and doubts of research. On the other hand, if a man pursues in turn several different lines of work, two of which are based on new technic created by him alone, it is not a question of choosing a problem but of creating one!

A superb experimenter, combining the talent of a magnificent surgeon and a shrewd observer; a dynamic lecturer, surpassed only perhaps by Maximov in logic and in the use of language; a powerful thinker, never interested much in priority, never influenced by any authority, he understands only the logic of facts. Constantly revealing new phenomena of life, he gives to them tentative explanations, binding them in harmonized theories. But never even in the heat of argument does he fail to distinguish between a fact and a superimposed theory, and he is always ready to discard the latter if it appears desirable to do so in the light of new evidence. His perfect memory is referred to by all who have had a chance to observe it, and it is this quality that enabled him to guide simultaneously the work of several institutions and supervise more than thirty problems at a time. Creating a spirit of enthusiasm in his co-workers; admired and loved by his pupils; respected by every one who comes into personal contact with him; just and impersonal in his judgment of men; never afraid to speak the truth and to admit it when told by others—such is Pavlov, and men like him are the greatest gift that a nation can bestow on humanity.

Pavlov himself ascribes his success to the ability to think constantly about the subject of his work, in this respect resembling Edison. Once, for example, he went with his wife to a new and much spoken of opera, *La Bohème*. When asked the next morning by Dr. Babkin how he liked it, he answered that he could not say definitely because, as he was thinking most of the time about conditioned reflexes, he really did not hear it. No matter how important or how trivial the subject of his thoughts, his concentration is extreme, and occasionally when interrupted in the process he goes into a violent rage, completely dismissing the incident later. A man of profound emotions, Pavlov possesses an intellect keen enough to keep them under control when necessary without inhibiting himself in everyday life. Quick in judging the characters of persons and events, he is seldom wrong. As characterized by himself, he has a mind turned toward reality, and it has never failed him and has unmistakenly guided him both in science and in social relations.

His long and healthy life Pavlov attributes to three factors: heredity, temperance and regularity of habits. He leads a simple and outwardly monotonous life and is extremely punctual and systematic. Coming into the laboratory on the stroke of the clock and leaving as punctually as he came, never breaking an appointment, no matter how interested he may be in a problem, he is true to his routine. On Sundays he sends every one away and sits alone in the laboratory observing the animals and thinking his never-tiring thoughts.

In summer he takes long vacations, spending three months a year in the country, gardening, playing his favorite game of *gorodkee*,

catching butterflies and doing most of his reading for the year; and in the autum he comes back to the city full of new energy, knowledge and ideas.

He married while young, and all the trivialities of everyday life have been gradually taken over by his wife. She has been solely responsible for the education of their children and the running of their home and, as reported by Savitch, has even for many years ordered all Pavlov's garments and shoes. As he almost never reads any newspapers or other periodicals, it is through his wife that Pavlov keeps in touch with outside life, and to her ability to surround him with comfort and peace he owes probably much of his energy and youthful enthusiasm. Although rather unpractical in the ways of life, Pavlov is not completely absorbed by his work. He is a great enthusiast in all sports and a great admirer of art, loves music, has read many a piece of fiction and is very hospitable.

The name of Pavlov is known and respected by all the civilized world today. Few scientists have acquired during their lifetime such honors and recognition. Many remarks in this brief sketch, if applied to other eminent scientists, might appear exaggerated, and yet they seem rightly used in regard to Pavlov.

The year 1935 finds him a thin, slightly bent little man with shrewd, thoughtful eyes, a man who has lived the most intense of lives, seen great progress and calamity, experienced great joys and disappointments and carried unchanged through it all perhaps only one single ideal—the love of truth.

CONSTANTIN VON MONAKOW
1853-1930

COLIN K. RUSSEL, M.D.
MONTREAL, CANADA

Constantin von Monakow was born on Nov. 4, 1853, on the country estate of Bobrezowo in the government of Wologda in the north of Russia. His father, Ivan von Monakow, who as one of ten children had inherited the property, lived here among his bondsmen when Constantin came into the world, and commanded his regiment among them according to the old patriarchal custom and tradition. The father had previously been a cabinet official, a censor in the department of education, and had as such lived from time to time in St. Petersburg. He had also traveled in foreign parts and had many intellectual interests, especially philosophy, history, literature and languages (among others, Greek and Arabic), which he earnestly pursued in his large library. Constantin's mother, Alexandra Leonette Dukschinski, was the daughter of a high official of Polish descent in St. Petersburg, so Constantin had already united in him at birth various ethical elements which proved to be a fortunate combination.

When 4 years of age Constantin experienced his first great grief, which struck very deeply. His mother, whose favorite child he was, contracted tuberculosis. With her death the ideal family life in Bobrezowo was destroyed. The afflicted father traveled in foreign parts and took up once more the state service. The education of the children was entrusted to distant relations and foreign governesses not always sympathetic with the boy's lively spirits. Two traits in his character became apparent very early, traits which are characteristic of his later life. One was a strong self-teaching trait, which he showed at 6 years of age, assimilating independently through listening to his elder sister's instruction in languages, and through examination of a child's reading book learning to write with printed letters. The other was a strong religious feeling and interest in religious questions, which was in keeping with the religious tone of the Russian life of that time, especially in the country. One particularly deep and inextinguishable impression was made on the 5 year old Constantin when he lay very

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Aside from the general acquaintance gained when I was a pupil working under von Monakow in 1903-1904, my information as to the facts of his life was obtained almost entirely from the biography written by his pupil, co-worker and successor Prof. M. Minkowski, published in the Schweizer Archiv für Neurologie und Psychiatrie (**27**:1, 1931) from which in places I have freely translated.

ill with scarlet fever and a distinguished elderly Greek Catholic priest appeared in full vestments and with assistants at his sick-bed to give him extreme unction. This event, which coincides with the beginning of an immediately perceived and from then on quickly progressive improvement, impressed him deeply; he prayed much. He liked to imitate religious ceremonies; he read eagerly the Old and the New Testament and at the age of 8 preached to boys of the same age to convince them—certainly without results—that a firm belief is sufficient to change one object into another, for example, a key into a horse. At school he became enthusiastic over Russian literature and geography. He showed an astonishing memory, learning much by heart easily. In other subjects, however, he appeared to have been an ordinary student, who on account of insubordination was little loved by his teachers.

The father, who belonged to the official Greek orthodox faith in form only, had made himself a political suspect since, in spite of his official position, he had embraced liberal democratic ideas, read forbidden foreign books and secretly condemned the Czar's regime. When this became known, his position was made untenable, if not distinctly dangerous, and he was compelled to leave Russia. Fortunately, he was able in the last hour to sell his property.

The family settled in Dresden, and Constantin entered the Krausse Institute and was taken into the sixth form. While handicapped by his imperfect knowledge of the German language, he made good progress in Latin and Greek and showed particularly musical talent and a lively interest in the theater.

With the outbreak of the Austro-Prussian War in 1866, the father felt himself out of sympathy with the country and again decided to move, this time to Zurich in Switzerland. Constantin, in the first class of the canton gymnasium, showed himself a flighty, indifferently gifted and little disciplined scholar. He apparently had difficulty in adapting himself to the arbitrary, systematically pedantic, dry, formal pedagogy, especially in the language classes. He preferred his self-teaching methods in the natural sciences, history, French and German literature and English and complained to his father about the tiresome and fruitless instruction.

About this time his sister Mascha, aged 17, died of pneumonic phthisis following an acute depressive psychosis. Her illness and death seemed to give rise to the idea that he would like to be a physician, and owing to her death he and his sorrowing father were brought somewhat closer together for a time. The years 1869 and 1870 he and his matic art. For some time he considered seriously becoming an actor. On returning to Zurich in 1870 he reentered the gymnasium, but his lack of success in examinations caused his father great dissatisfaction,

and in order to carry out his studies in his own way he left home. He was especially interested in learning Greek and would begin his studies at 5 a. m. He was interested, too, in Shakespeare and Heine. Physics and chemistry did not interest him much. He taught himself to play the harmonium and composed songs and sonatas. This remained a pleasant hobby for his spare hours throughout life.

In 1872 he barely passed his final examinations at the gymnasium and registered in the medical faculty in Zurich against the advice of his father, who had no great opinion of medicine. Constantin himself had no particular scientific interest in it, but felt that it would soonest lead him to independence.

Interested in philosophy, the history of art and literature, he, with some older colleagues of other faculties, formed a club called "The Omnipotentia," at the meetings of which all sorts of discussions were held with enthusiasm. He dissected animals and did some vivisection in his lodging. He studied histology and embryology with Professor Frey; physiology with Hermann, who impressed and interested him keenly, and anatomy with Hermann Meyer. The course in the anatomy of the brain and spinal cord, in which it was still taught that the site of the soul was in the corpus callosum in which more wax models than real brains were used, did not interest him. After going three times to these classes he never went back and never had any systematic instruction in the anatomy of the brain.

In the sixth semester he became a junior assistant to Ebert in pathology and had good opportunities to study macroscopic and microscopic pathologic anatomy, and in 1876 he became acting assistant in the psychiatric clinic of Burghölzi under Hitzig, who in 1870 had discovered the electrical excitability of certain parts of the cortex and had thereby initiated the first exact experiment on localization of function in the brain. He was soon put in charge of the male division of the clinic, made some histologic studies of the brain in various types of dementia, and did some experimental work on the liver and brain in chloroform poisoning that showed hypertrophy and fatty degeneration of the liver and changes in the cerebral vessels. This work was interrupted by an epidemic of typhus.

He showed so much interest in the organization and practical care of the mentally ill that Hitzig sent him on a three weeks' trip to similar institutions in Germany and paid his expenses. In the Griesing Institute in Munich, the director, von Gudden, who during two years in Zurich as director of the Burghölzi had done much to encourage Monakow in his scientific interests, now showed him for the first time serial sections through the whole brain cut with von Gudden's microtome. Here he saw first definite secondary atrophy of the anterior corpus

quadrigeminum after enucleation of an eye in a cat, and also secondary atrophy of the optic thalamus after partial destruction of the same hemisphere. Gudden also showed him microscopically secondary atrophy of the sixth nucleus after section of its nerve.

This was the important achievement of the new and unrivaled method of producing secondary atrophy, and with his intuition for everything essential and important, the richly endowed, keen young medical student received a deep and lasting impression not only of the investigator but of the wonders of the investigation which he had opened to him.

In March 1877 he passed his final state examination, but this otherwise happy event was clouded by a complete break between him and his father. On his return to Zurich after a short trip to Northern Italy with his friend and future brother-in-law, Ferdinand Rudio, he found himself entirely on his own resources. He tried to obtain an assistantship in a hospital, but as every one of these seemed to be taken he decided to start as a practicing physician in his room in a boarding-house. In the course of six weeks he did not see a single patient, so he decided to leave Zurich. He obtained a position as ship's doctor on a vessel sailing for Brazil and the Argentine. On his return from this trip, in January 1878, he obtained an appointment as assistant physician in the small hospital for mental diseases of St. Pirminsberg in the village of Pfafers in the canton of St. Gaul, Switzerland. In this provincial hospital, which had been established in an old Benedictine cloister in the middle of the mountains, he spent the next seven years, which were among the most productive of his life. He acquired a von Gudden microtome. The brain was hardened in formaldehyde and fixed in chromic acid and was held by a mixture of stearin, pig's fat and suet. This was melted and poured in between the brain and the surrounding metal cylinder, where it soon hardened. The brain was cut by a long two-handled draw-knife under water.

It was about this time that he learned of cortical mind blindness following the destruction of the occipital lobes, described by Hermann Munk, and he was able to correlate this with the anatomic facts which he had been shown by von Gudden. He began by experimentation and the method of producing secondary atrophy, and in 1879 destroyed the occipital lobe in two new-born rabbits and kept them alive for more than a year. The brain was then to be cut in series, but when the pieces were being hardened in chromic acid he happened to cut a fresh surface with a razor through the level of the anterior corpora quadrigemina. Not only this was reduced in size, but the corpus geniculatum externum, about the connections of which no more had been known than that after enucleation of an eye of a rabbit atrophy of the corpus geniculatum

externum on the opposite side occurred, as well as atrophy of the anterior corpus quadrigeminum. In his experiments the external geniculate body on the side of extirpation of the occiptal lobe was reduced to a small remnant as compared with that of the opposite side. The complete disappearance of the ganglion cells of this nucleus as the result of the destruction of the occipital lobe or the radiations of Gratiolet was quite different from the secondary degeneration in it following destructive lesions of the optic nerve or tract or the enucleation of

CONSTANTIN VON MONAKOW
1853-1930

the eye. In this form of atrophy there was disappearance of the fibers of the optic tract and of the intercellular ground substance, while the ganglion cells were not degenerated as after the occipital destruction but there was simple reduction of volume only or atrophy without more essential changes. He thus showed that the optic nerve took origin from ganglion cells in the retina. Phylogenetically, the primary optic center was in the anterior corpora quadrigemina, and later the external geniculate body was added. The latter originated a new relay to the occipital cortex. Monakow thus demonstrated the anatomic foundation for Munk's clinical observation. In spite of difficulties such as would be

met with in a country hospital for mental diseases—the distance from all scientific centers and the inadequacy of available implements—it was here that this great man with his inexhaustible energy made some of his finest anatomic discoveries.

Following demonstration of secondary atrophy of the external geniculate body after destruction of the occipital lobes, study of the extirpation of other parts of the cortex followed logically, and he thereby established that the thalamus was made up of various nuclei which were projected to more or less definite parts of the cortex, as had been previously asserted by Luys. He first differentiated and localized the nuclei of the thalamus in animals and in man, and although many refinements in the description and modifications of the terminology have been made since, the conception of the so-called projection of the thalamus on the cortex remains fundamentally as Monakow described it.

In 1880 he married Matilda Rudio of Wiesbaden, the sister of his friend, the professor of mathematics of the Polytechnic in Zurich. They were very happy; she was a great comfort to him and helped him with his microscopic preparations. One son and two daughters were soon born of this union.

The results of the operative approach to the cerebral hemispheres encouraged Monakow to try the same method in the fiber pathways of the brain. Hemisection of the upper part of the spinal cord of a rabbit caused disappearance of the large ganglion cells of Deiters' nucleus. This was the foundation for the acceptance of the deiterospinal or vestibulospinal tract. Another important discovery followed the production of a destructive lesion in the parietal region of a cat which involved the inner capsule. He established not only secondary degeneration in the lateral and ventral nuclei of the thalamus but, what is more interesting, atrophy of the fillet, which he followed through the internal arcuate fibers and the crossing to the nuclei of the posterior columns of the opposite side. This gave him the opportunity to trace the fillet from its origin in the posterior columns (which Meynert and Flechsig and Wernicke had presumed and which was generally accepted) to its probable ending in the optic thalamus and to establish here an intermediate station on its way to the cortex. He demonstrated the different cellular layers of the cortex, distinguishing especially between projection and association parts, throwing new light on the cortical fibers which was fully appreciated only later with the progress of knowledge in cell architecture.

Finally, while at the St. Pirminsberg hospital, he made an important discovery with regard to the acoustic tract and the rubrospinal bundle. Following a lesion of the lateral fillet he found, on the one hand, ascending secondary degeneration up to the ganglion of the posterior corpus quadrigeminum and, on the other, descending degeneration in the dorsal

part of the superior olive on the same side and of the striae acusticae and the miter-formed cells of the tuberculum acusticum of the opposite side, besides descending degeneration down to the lateral column of the spinal cord, which later was called the rubrospinal bundle of von Monakow. He wisely waited several years, until 1889, until he had verified these findings in a dog before he published them. This formed a starting point for the organization of the pathways of hearing, which later was confirmed and added to by other workers (Winkler, Fuse, Brewer, Brun, Nagino). The mere enumeration of such findings cannot inspire the same interest today as it did to scientists of that period, and Monakow about this time decided to move to Zurich; in preparation for this move he spent several months in Berlin, where he attended Westphal's clinic at the Charité and those of various other leading physicians of the day. He came in close relationship with Munk, who gave him several brains of animals that he had operated on and continued to send him such specimens showing experimental lesions after he arrived in Zurich. His scientific establishment in Zurich in 1885 was not without its difficulties. Professor Klebs, chief of the Pathologic Institute, allowed him to have a table in a room, but he had no help. However, he was greatly encouraged when H. Donaldson, who later became director of and professor at the Wistar Institute for anatomy and biology in Philadelphia, registered as a student and was willing to work under his guidance. Professor Klebs, under certain conditions, allowed him a little used experimental room as his private laboratory, and here he and Donaldson worked, cutting serial sections on Munk's experimental animals. Here was laid the foundation for the present *Gehirn-Anatomische Institut* of the University of Zurich. Brains were sent to him for examination by his colleagues in Zurich and in Germany, and further experimental work was undertaken.

In 1887, in association with an eye specialist and an ear specialist, Monakow, as neurologist, undertook the founding of a private polyclinic. It was a new venture in Switzerland and did not meet with the entire approval of internists, particularly, who considered it an inopportune innovation. Its humble beginnings in two small and simple rooms in the lower town, however, formed the basis of what is today the State Polyclinic. In 1891 he published a short description of a 7 month anencephalic human fetus, and with this began his interest in maldevelopments of the central nervous system. In the same year he published an article entitled "Discussion of Cortical Hemianopia with Alexia." In 1895 appeared his great experimental, pathologic and anatomic work on the tegmentum, the superior colliculi and the subthalamic region. This was based on study of secondary atrophies following destruction of the cerebral hemisphere in new-born animals, a dog and a cat, and in two cases of long-standing destructive lesions of

the cerebrum. Among many other things, in this work he established the end-division of fibers of cortical origin in the pontile gray matter, which degenerated secondarily to the cerebral lesion, while the ganglion cells of the pontile nuclei showed a simple reduction in volume.

Monakow recognized immediately the value of Edinger's work on the comparative anatomy of the nervous system of lower animals and incorporated those findings with his own experimental and clinical observations.

In 1897 the first edition of his "Gehirnpathologie" appeared in Nothnagel's handbook, and eight years later the second, a larger and more complete edition—a lasting memorial. It was not a compilation of the literature, but the results of his own and his pupils' observations over many years in normal anatomy, experimental research, clinical cases and pathologic anatomy. In the section on physiology he expounded his theory of diaschisis, that is, the splitting off of one part from another and of more lately acquired functions under the influence of shock. He showed by examples from his experiments in extirpation and from clinical cases the difference between the initial and transitory symptoms and the residual and permanent disability.

His publications at this time treated of such subjects as cyclops with reduplication of the spinal cord, a case of microcephaly, a consideration of apraxia, posthemiplegic disturbances of motility and secondary changes in the spinal cord following an old lesion in a brachial plexus. In 1899 he brought out a small work on subtentorial neurofibromas, reporting three cases of tumors of the cerebellopontile angle, being the first to point out the operative possibilities of these tumors. In 1901 he wrote a comprehensive report on malformations of the nervous system. In this he attempted to work out more exactly the different forms of disturbances in development, comparing them with the normal and using the facts discovered in the malformations to throw light on the normal development and architecture of the brain. He then developed the theory of genetic compensation, i. e., the eventual compensatory hypertrophy of synergistically related structures.

In 1904 he was made member of the Inter-Academical Brain Commission, which had been founded by His in 1901 and which consisted of thirty members chosen from all countries. Monakow's institute was recognized as the central Inter-Academical Research Institute.

In 1907, with Oppenheim, Bruns, Edinger, and Moebius, he founded the Association of German Neurologists. In 1910, with Dubois, he founded the Swiss Neurologic Association. In 1910 also appeared his large monograph on the red nucleus, central gray matter and hypothalamic region in man and other mammals, based on experimental and clinical observations. He pointed out the gradual development of a small cell part of the red nucleus in the scale of animal development,

with a simultaneous gradual diminution in the large cell nucleus. He described the special types of secondary degeneration of these nuclei following different lesions in the cord, central gray matter, cerebellum, midbrain, thalamus and cerebrum, showing the relationship of these different parts with the rubrospinal tracts and especially the phylogenetic displacements in the ascending scale of animal development, as a part of a general cephalad displacement of function. In 1910, for the meeting of the German Neurologic Association at Innsbruck, he assembled, analyzed from a developmental point of view and discussed the localizations of the different types of movement, especially in man, from those on which life depends, such as breathing, sucking and swallowing, the crude defensive movements and the locomotor reflex movements up to the goal, or skilled movements, and the movements of expression, such as speaking and writing. It was obvious that every type of movement was made up of phylogenetic and ontogenetic old and new components of different values, localized at different levels of the nervous system, and he developed his so-called chronogenetic theory of localization.

The outbreak of the World War naturally influenced greatly the productivity of the school in the *Gehirn-Anatomische Institut,* and while important work was being turned out by Uemura, Fukuda, Minkowski, Brun, Tramer and Meier-Muller, other workers had to return to their own countries. On account of the war the transactions of the institute could no longer be published, as formerly, in Germany, and so in 1917 Monakow founded the *Schweizer Archiv für Neurologie und Psychiatrie.* He was editor-in-chief until his death.

The effect of the war on the master was extraordinary. His interest in neurology and anatomy of the nervous system and in all the medical problems in which he had been engrossed for forty years dropped into the background. He put all these aside and devoted himself to the study of history, politics, psychology and psychopathology, ethics and philosophy. His deeply religious feelings, which from childhood were engrafted into his personality, awakened to new life. He withdrew from his practice and society and, for a time, from his familiar friends, and spent a period of contemplation and meditation among small villages and in association with simple, natural persons. After his return to the clinic, whereas formerly his chief concern had been in organic disturbances and such problems as aphasia, apraxia and agnosia, his interest now seemed to be awakened in psychologic and philosophic problems and the neuroses, as though he hoped that he might find in these fields some important elements that would throw light on the tragic neurotic crisis through which the world was passing.

As was to be expected from a man of his great originality and energy, he soon produced a series of works of a psychologic and philo-

sophic character which show originality and courage. Although Monakow's claim to fame must be based on his contributions on the anatomy and physiology of the nervous system, one must, in spite of limited space, at least refer to his publication in 1928 in association with E. Mourque of "A Biologic Introduction to the Study of Neurology and Psychopathology; the Integration and Disintegration of Function."

One cannot but be filled with admiration at the courage of the man and the completeness of his attempt to cover the whole field of the nervous system. In an essay entitled "The Value of Life," which he was writing at the time of his death and only a few minutes before he drew his last breath, the last words that he wrote were *angemessenes Handeln,* and one must feel that as a scientist and a worker his life to him must have been, as it has been to the world, a satisfactory endeavor.

One feels that this great man, with his keen interest, his intelligence, his inexhaustible energy, omitting no means of approach that might lead to the truth, by his steadfastness and importunity made Nature unveil to him, at least that part in which he was interested, more than to most men.

Abstracts from Current Literature

POINTS IN THE SURGERY OF THE FRONTAL LOBES OF THE BRAIN. JAMES R. LEARMONTH and HAROLD C. VORIS, Arch. Surg. **27**:506 (Sept.) 1933.

This article is an exposition of some of the main anatomic and physiologic points which concern neurosurgical procedure in cases of lesions in the anterior cranial fossa. It is an attempt "to combine in broad outline an account of the surgical difficulties which are the sum, or perhaps even the product, of lesion and site." Learmonth and Voris review briefly some points in connection with the anatomy of the coverings of the anterior fossa, including the frontal sinus, the arrangement of diploic veins and the arrangement of the dura and its vessels. Admitting that it is traditional to lay stress on avoiding the frontal sinus, they "have never seen harm result from opening it; such an opening may be plugged with bone wax or covered with animal membrane (Adson) but if the mucous membrane is intact a small bit of muscle is enough." The arrangement of the diploic veins with relation to bleeding from the edges of the bone is pointed out. Bone wax is always necessary to check oozing from the cut outer end of the greater wing of the sphenoid which results from the anastomosis between diploic veins, meningeal veins and the sphenoparietal sinus. The bone flap is supplied by branches from the deep temporal and the middle meningeal arteries. Stripping the temporal muscle from the greater part of the flap to lessen the risk of postoperative extradural bleeding rarely jeopardizes the vitality of the flap.

If the diploic veins are very large, a broad groove can be cut with forceps in place of the Gigli saw, so that each canal can be plugged with wax. The authors also advocate this in isolating a portion of skull invaded by meningioma. They recommend splitting the dura (Elsberg) to obtain gradual decompression in cases in which the latter cannot be opened safely on account of high intracranial tension. The line of cleavage is most easily obtained toward the base.

To expose adequately basofrontal or hypophyseal growths it may be desirable to remove the anterior end of the frontal pole. This is done as seldom as possible, but the authors have noted no "prohibitive degree of intellectual impairment" as a result. "The watershed between the territories of the anterior and middle cerebral arteries forms a convenient line to mark the limits of amputation." The edges of the incision should extend well within the territories of both. When possible, incision of the cortex should be made parallel to the vessels.

Ligation of cortical veins is rarely unavoidable, but occasionally their upper ends course over a tumor from which they cannot be separated. The extent of resulting paralysis varies with the venous pattern. In one case ligation of the upper end of the precentral vein was not followed by any gross paralysis; in another ligation of the lower end was followed by hemiplegia, which improved in time; in a third, tying the superior branch of the vein of Trolard during removal of a parasagittal meningioma caused a permanent brachial monoplegia.

Ventriculography or ventricular puncture may be required for final localization of a tumor under the following conditions: "(1) when it is certain that an intracranial tumor is present, but no localizing feature can be found; (2) when, as not infrequently happens, the clinical picture is in keeping either with a tumor of one frontal lobe or with a tumor of the opposite cerebellar lobe, and (3) when it is tolerably certain that a tumor is growing in one of the frontal lobes, but there is doubt as to the side." Tumors near the foramina of Monro may obstruct the flow of cerebrospinal fluid from one or both ventricles, resulting in their dilatation, which is often unequal and then greater on the side opposite the growth. When it is anterior in the lobe, dilatation is absent and the ventricle on the same side may contain much less fluid than normally. A tumor of the frontal lobe gives a char-

acteristic filling defect in the corresponding anterior horn of the lateral ventricle. If large and on the mesial aspect of the lobe, a similar defect may also be seen on the opposite side. "This pressure must be transmitted through the falx cerebri, and the occasional occurrence of those contralateral filling defects shows that the falx is by no means a rigid partition."

In some instances it is best and often quickest to tap both ventricles. A small ventricle with but a few cubic centimeters of fluid on one side rules out a diagnosis of cerebellar tumor and also lateralizes the growth. When both ventricles are dilated it is wiser to proceed with the injection of air, as only thus can a diagnosis be made between supratentorial and infratentorial growths. Though the dilatation may be so marked as to lead to a suspicion of an infratentorial growth, if it is in a frontal lobe its presence will be shown by the filling defect in the lateral ventriculogram. When the filling defect is bilateral the ventricles are displaced away from the side of the growth or of the largest growth if the tumor is bilateral. When xanthochromic cerebrospinal fluid is obtained by ventricular puncture it is likely that the tumor impinges on or invades the ventricular system.

The authors review briefly, with the aid of diagrams, the various surgical approaches to the anterior cranial fossa. They describe more fully one technic "not as an improvement on other methods but as a procedure which has been satisfactory in every way. . . . The incision passes across the head, in the line of the coronal suture; the advantages of an incision of this type have been enumerated by Souttar." Briefly, the scar is within the hair line; the incision occurs between the territories of the internal and external carotid arteries, and the line of incision is not superimposed on the incision in the skull. "It is often unnecessary to make the long tragus-to-tragus incision described by Souttar; this is indispensable only when it is possible that a bilateral exposure may have to be secured." For a unilateral approach, e. g., for hypophyseal adenoma, "the incision may be stopped half-way between the median line and the tragus of the opposite side; an additional incision perpendicular to this and passing anteriorly to the hair line may be added, or the incision may be slanted, so that it begins at the tragus and ends at the hair line of the opposite side, midway between the median line and the zygoma." When placing skin towels the authors attempt to catch simultaneously the temporal vessels by one of the sutures and to place another in line with each supra-orbital artery to minimize bleeding. On the anterior edge of the wound they use the skin clips employed by Adson, which are less cumbersome than the hemostats used on the posterior edge, which aid also in retraction.

Several paragraphs deal with the question of how radical an operation one ought to perform. The possibility of aphasia and change of intellect are considered especially. In general, the authors have found that "whether the defect in speech is the result of pressure on, or actual invasion of, Broca's area, the risk of producing permanent and complete aphasia is rarely so great as to prohibit a radical attack on a relatively benign growth. . . . it has been the collective experience at the Mayo Clinic, that primary frontal lobectomy for tumor has been almost invariably followed by some degree of permanent mental impairment, which sometimes has been so extreme as to be socially and economically objectionable. . . . Tumors confined to the pole of the lobe can be removed without much risk of intellectual impairment, and for this there are developmental and architectonic reasons. When the tumor occupies the body of the lobe, the decision is more difficult. When the tumor is cystic, or when it is partially or wholly encapsulated, it is likely that the fibers about it have been displaced and compressed, and thus physiologically blocked; in these circumstances, a radical attempt at extirpation is likely to be followed by restoration of function rather than by further impairment. . . . On the other hand, ill defined tumors such as astrocytomas grow between the fibers, often without compromising their function, and any attempt at extirpation must perforce include with the tumor tissue physiologically intact cerebral pathways. Large tumors of this histologic nature are probably best treated by decompression only, for their life history is so prolonged that the interests of the patient are best served by relief of the increase in intracranial pressure; as

Holmes has emphasized, many 'mental' symptoms are due wholly to generalized increase in intracranial pressure. Paradoxically enough, in the case of the most malignant spongioblastoma multiforme, its pseudo-encapsulation suits it for subtotal removal, as providing the greatest relief during the short period which its host has still to live."

If the tumor is composed of blood vessels, the authors agree with Bailey and Cushing that it should not be attacked directly. They treat these lesions by decompression and adequate roentgenotherapy. When the intracranial part of the operation is completed, the writers cover with Cargile's membrane any part of the cortex uncovered by dura. The membrane is shaped to lie beneath the edges of the dura and is kept in place by replacing the dural flaps over it. It is not used at any point where it might interfere with a subsequent puncture of a cyst.

The authors favor drainage of flaps through a stab wound and also direct drainage of the skin wound for forty-eight hours, the drains being shortened after the first twenty-four hours. They state: "Surgical drainage of craniotomy wounds is a bogey which should be stripped of its terrors; we have never seen any infection as a result of it, or any prolonged leak of cerebrospinal fluid, and we have never had to deal with postoperative hematoma in a case in which a drain had been used." Some points concerning postoperative management are also discussed.

From 1914 to 1931, 180 cases of tumor involving one or both frontal lobes were verified histologically at the Mayo Clinic at operation or necropsy. Of these, 162 were observed from 1922 to 1931. Many cases were excluded in which a glioma was probably present but not verified. There was a high percentage of meningioma in the frontal region, 41.7 per cent, which is in contrast to 13.4 per cent occurring in Cushing's series for the brain as a whole. This is explained by the occurrence of two basal sites of election for such growths in the frontal region, i. e., the meninges covering the olfactory grooves and those in the neighborhood of the sella turcica. Of the 75 meningiomas, 33 were situated on the convexity of the lobe, 21 were parasagittal, 5 were suprasellar and 16 were attached to the olfactory groove.

Rounded, wholly intradural growths presenting solely on the outer surface of the lobe are easiest to remove. Involvement of the skull and scalp increases the technical difficulty of removal. Replacement of the tumorous bone after boiling (Naffziger) has been used successfully (by Craig). In the case of parasagittal growths, when it seems advisable to increase exposure by incision of the brain, advantage may be taken of the vascular watershed; thus the growth may be uncapped by removal of the edge of the lobe supplied by the anterior cerebral artery. Though this incision breaks the rule that an incision into the brain should be parallel to its arteries, it is nevertheless parallel to the association tracts. Bilateral parasagittal growths are the most difficult to deal with. The authors discuss the difficulties of removing suprasellar meningiomas. Occasionally one follows the arteries in its growth, so as to form a tumorous sleeve for them. In one case the only vessel in the circle of Willis not enclosed by tumor was the left posterior communicating artery. Meningiomas of the olfactory grooves are generally operable. They may ultimately invade the lateral mass of the ethmoid, in which case the lower part of the growth is left. To obtain adequate exposure of large growths in this region it is suggested that uncapping the frontal lobe through the arterial watershed may be useful.

Of a total of 90 gliomas, 42 were spongioblastoma multiforme; 17 were astrocytomas, of which 6 were cystic and contained a removable mural nodule. Regarding solid gliomas, the authors believe that the smaller the tumor and the more anteriorly it is situated, the more radical extirpation should be. For the larger and more ill defined growths that approach the rolandic fissure they prefer decompression alone. Furthermore, there seem to be a number of growths diagnosed as astrocytoma by quick methods, whereas sections taken elsewhere from the tumor show areas characteristic of spongioblastoma multiforme.

ELVIDGE, Montreal, Canada.

THE PATHOLOGIC ANATOMY AND PATHOGENESIS OF EPILEPSY. M. MINKOWSKI, Jahrb. f. Psychiat. u. Neurol. **51**:134, 1934.

Minkowski comments on the difficulties encountered in evaluating the pathogenic significance of the more common chronic pathologic changes in the blood vessels, nerve parenchyma, neuroglia, ependyma, choroid plexus and meninges in cases of chronic genuine epilepsy. In a considerable number of cases these changes are undoubtedly the sequelae of repeated epileptic seizures and represent a summation or accumulation of acute changes in the course of individual seizures. This is especially the case with the chronic vascular changes consisting of proliferations and thickenings of the walls of the vessels, particularly of the adventitia, in the smaller vessels and precapillaries so frequently observed in the brains of patients, even young persons, with chronic epilepsy. These changes may be readily explained on the theory of repeated marked variations in vasomotor tone, volume of the vessels, blood pressure and permeability of the walls of the vessels, especially when one accepts Ricker's recently presented theories as to the prolonged effects of even a single cerebral trauma on the irritability of the cerebral vasomotor system. In contrast to the causation of the alterations in the vessels it is questionable whether the chronic changes in the nerve parenchyma and neuroglia found in the brains of epileptic persons can all be attributed to a summation of acute changes in the course of the epileptic paroxysms.

The development of the well known sclerosis of the cornu Ammonis in many cases of chronic epilepsy is attributed by Spielmeyer, Scholz and others to repeated attacks of acute circulatory disturbances in the nature of angiospasms during the seizures. On the other hand, other observers believe that there probably exists a constitutional factor which renders the cornu Ammonis less resistant to various noxae. Bratz, Steiner, Astwarzaturow and others believe that an early developmental disturbance or a chronic pathologic process probably exerts certain deleterious effects on this structure, even regardless of the seizures, and that these effects are to a greater or lesser extent cofactors in producing the sclerosis.

Changes in the cerebral cortex in chronic epilepsy have been the subject of numerous investigations. Some of these changes, such as accumulations of lipoids and other sclerotic and atrophic degenerative changes in the ganglion cells, disappearance of the intracellular fibrillae and destruction of cells in foci or even in entire layers, together with the chronic changes in the cortical vessels, have not been sufficiently constant and uniform to be regarded as the essential factors in the pathogenesis of epilepsy. The same is true of such changes as deviations in the architectonic structure of the various cortical layers, abnormal size or defective differentiation of certain types of cells, the persistence of embryonal cells and other dysplastic phenomena due to constitutional or early developmental defects. While these are not to be regarded as the pathogenic factor, nevertheless Minkowski believes that their significance must not be entirely disregarded.

Chronic alterations in the cerebellum, such as degeneration and destruction of the Purkinje cells, atrophy of the cerebellar convolutions, degeneration of the dentate nucleus and changes in the olives, have been found in cases of epilepsy by the author as well as by numerous other observers, but they have also been observed in cases of nonepileptic diseases.

Chronic changes in the glia, the well known marginal gliosis and perivascular gliosis, offer no better insight into the pathogenesis of epilepsy. Whereas Chaslin first regarded marginal gliosis as a constitutional glial proliferation and, as such, the cause of epilepsy, subsequent observers, among them Bleuler and Alzheimer, regarded the gliosis as a secondary phenomenon—a reaction to the destruction of the nerve parenchyma. Still other observers, for instance, Jakob and Bielschowsky, have taken an intermediate position and have considered marginal gliosis as the combined result of a primary increased tendency of the glia to proliferate and a secondary activation of or reaction to a degenerative process of the nerve parenchyma. The latter view appears to Minkowski to be the most plausible.

The pathologic changes common in the choroid plexus, the ependyma and the subependymal tissues in the brains of epileptic patients are next discussed. While

these may be of some significance, because they may be evidences of a congenital or acquired hypoplasia or dysplasia or of a chronic intoxication of the brain, they cannot be regarded as specific or pathognomonic of epilepsy; similar changes are observed in diseases other than epilepsy and even in normal brains.

Various authors have stressed the serofibrinous or cystic arachnoiditis which they observed in many cases of epilepsy. This change is variously interpreted as being the result of a meningo-encephalitic process early in life, of a latent cerebral trauma or of an acute accumulation of cerebrospinal fluid during the seizures. In this connection, Minkowski also discusses the theories advanced by American neurologists who claim that in genuine as well as in symptomatic epilepsy there occurs a stasis of the cerebrospinal fluid in the meninges as a result of a constitutionally defective development or pathologic changes in the pacchionian bodies, which are regarded as important structures for the drainage of the cerebrospinal fluid. According to this theory, the increased pressure in the trabeculated and adhesive arachnoid membrane irritates the subjacent cortex and produces convulsions. At any rate, there is some evidence that humoral, secretory and hydrostatic factors play some rôle in epilepsy, the precise nature of which remains to be determined. It is of interest to note in this connection that Orzechowski believed that general or localized disturbances in the circulation of the cerebrospinal fluid are probably the most common primary epileptogenic factor. Salmon, likewise, attributed great significance to the quantitative and qualitative alterations of the cerebrospinal fluid in association with functional anomalies of the choroid plexus in the production of epileptiform seizures. The frequent occurrence of seizures in cases of uremia, alcoholism, lead poisoning and other intoxications, this observer believed, confirms his hypothesis; he emphasized the rôle played by the activity of the choroid plexus in relation to the function of the endocrine glands, especially the hypophysis, and of the vegetative nervous system. Stohr demonstrated long ago the presence of an unusually rich network of sympathetic terminal fibers in the choroid plexus. From these facts it seems that during a seizure there occurs an acute irritation of the vegetative nervous system which enhances the activity of the choroid plexus and the secretion of the ventricular fluid, with resulting increase in its pressure leading to dilatation of the ventricular system, especially of the third ventricle. According to Salmon, the acute dilatation and irritation of the wall of the third ventricle also affect the infundibulum and tuber cinereum in which there are supposed to be located, in addition to other vegetative centers, an epileptogenic diencephalic center which is particularly sensitive to quantitative and qualitative changes in the cerebrospinal fluid.

Minkowski next points out that the histologic changes in internal organs, especially in the endocrine glands (thyroid, parathyroid, hypophysis and suprarenals) in cases of genuine epilepsy do not occur with sufficient constancy or uniformity to be regarded as determinants in the pathogenesis of this disease.

From all this Minkowski concludes that in the present state of knowledge pathologic anatomy offers no satisfactory clue as to the nature of the basic pathogenic factor in the production of epileptic seizures. Most observers assume that the basis of genuine epilepsy must be sought in a general functional dynamic disturbance. Minkowski believes that this disturbance is not merely one of faulty balancing between irritative and inhibitory processes in the nerve centers, but that it is rather in the nature of a disturbance in the basic functions of the nervous system, i. e., disturbances in the receptivity, conductivity, irradiation and concentration of stimuli in the nerve parenchyma leading to disturbances in the general or specific effector responses, so that the latter become very difficult, slow, inhibited or otherwise disorganized. Such a disturbance must be based on faulty developmental factors at various levels of the nervous system, which may be congenital or acquired. The occurrence of such constitutional anomalies, especially the dysplasias in the cerebral cortex and in other neural structures in so many cases of genuine epilepsy, seems to favor this hypothesis.

With this theory in mind, Minkowski offers the following theory as to the pathogenesis of the seizures in cases of genuine epilepsy: The disturbances in

conductivity and irradiation of stimuli in the cerebral hemispheres produce an abnormal concentration and accumulation of stimuli in definite regions or layers of the cerebral cortex itself, in the so-called projection zones of the latter or in the brain stem, especially in the central gray masses around the ventricles and the aqueduct of Sylvius—the generally accepted central stations of the vegetative nervous system; this gives rise, on the one hand, to an increased motor irritability of the cortical apparatus and, on the other hand, to various disturbances of the central vegetative system, such as vasomotor disturbances, metabolic changes, alteration in the internal secretions and changes in blood pressure and in cerebrospinal fluid pressure—phenomena that are generally accepted as characteristic for epilepsy in general and for the preparoxysmal period in particular.

The type of elementary functional disturbance of the central nervous system constituting the site of origin of the genuine epileptic process may be hereditary—i. e., constitutionally preformed—or acquired early in life—i. e., in association with a pathologic cerebral process which may have been vascular, inflammatory or toxic and which occurred during fetal life or in infancy, leaving slight or no residua which can be demonstrated anatomically. As various noxae in the course of the development of the organism are capable, regardless of their special effects, of producing a general developmental inhibition or a reduction of the organism's resistance against later damage, it is obvious that these same noxae may produce not only functional disturbances but also morphologic abnormalities in the nature of various dysplasias of the type not infrequently found in the brains of patients with genuine epilepsy. In this connection it must also be remembered that there may exist in these brains finer morphologic changes which cannot be demonstrated with the histologic technic at present available.

If this conception is basically true, one may assume a sufficiently intense elementary functional disturbance in the brain, including not only the nerve parenchyma but also the neuroglia, ependyma and choroid plexus to produce endogenously paroxysmal epileptic discharges; when this basic functional disturbance is of lesser intensity the superaddition of any of the many accessory factors, which may be humoral, hormonal, vasomotor or psychic, may have the same effect.

The disturbances of the vegetative system, especially the vasomotor crises, the significance of which in the occurrence and in the course of epileptiform seizures is today generally accepted, may be regarded in the light of this conception of epilepsy as arising when the functional disturbance has reached the brain stem, where after a period of "preparation" corresponding to the preparoxysmal prodrome in the vegetative sphere it advances to a full-blown epileptiform seizure. In this sense attacks of petit mal may also be regarded as abortive paroxysms during which chronic irritation, especially of the vegetative centers, leads to a sudden vasomotor crisis which, owing to its short duration or to insufficient "preparation" of the motor apparatus of the brain, never leads to a somatic motor discharge.

Psychic manifestations in cases of epilepsy are complicated features of the disease. The most common are those in connection with the seizures themselves; next in frequency are the psychic equivalents, and next, the so-called epileptoid constitution. The epileptoid constitution, Minkowski believes, is the result of the elementary functional disturbances of the cerebral cortex with their baneful effects on the intellectual life of the patient. The affective anomalies of the epileptoid constitution also find their physiopathologic correlation in disturbances of vegetative and humoral factors which are so essential for the affective life. Periodic psychic disturbances may accompany or precede the epileptic attacks and sometimes are in the nature of psychic equivalents, which represent a discharge from the higher brain centers which, instead of being in the form of the usual motor discharge, appears in the form of fugues and unmotivated impulses leading sometimes to violent and dangerous conduct.

In so-called traumatic epilepsy, the attack-producing factor is to a considerable extent some pathologic process, which may be traumatic, vascular, infectious, neoplastic or otherwise. Any of these processes may give rise to prolonged dis-

turbances in the internal functioning of parts or of the entire brain. Of course, in all such cases constitutional or early acquired peculiarities in the structure of the brain may play a more or less important rôle in the production of the seizures. In this sense the pathogenesis of this form of epilepsy may be said to be identical with that of genuine epilepsy.

KESCHNER, New York.

ANEURYSMS OF THE CIRCLE OF WILLIS. PAUL H. GARVEY, Arch. Ophth. **11**:1032 (June) 1934.

This paper is in the nature of an ophthalmologic review covering material relative to aneurysms in the blood vessels forming the circle of Willis. In addition to the review, Garvey reports 5 cases in detail.

In 1859, Sir William Gull called attention to the relative frequency of intracranial aneurysms and their clinical manifestations. After a survey of previously reported cases and discussion of some additional cases of his own, he concluded: "Although we may from the circumstances sometimes suspect the presence of an aneurysm within the cranium, we have at the best no symptoms on which to ground more than a probable diagnosis." Beadles, writing over fifty years later, arrived at the same conclusion after analyzing 555 cases of intracranial aneurysm. He stated: "Only two or three have ever been diagnosed during life, and even in these cases it can scarcely be said to have been an absolutely certain diagnosis." Fearnsides, in 1916, maintained that while the original statement of Gull still held true there were cases in which multiple leakage of blood occurred owing to partial rupture of the aneurysmal sac and that in such cases clinical manifestations appeared, rendering a diagnosis not difficult.

In Garvey's 5 cases the clinical signs and pathologic changes are reported. In the third and fourth cases, the clinical syndrome had been ascribed to meningovascular syphilis and to a cerebral tumor, respectively. In the fifth case the patient is still living, but Garvey thinks that the diagnosis of aneurysm is certain. The patient was admitted to the hospital with an evident picture of subarachnoid bleeding. Lumbar puncture yielded a bloody spinal fluid under a pressure of 100 mm. of water, with 360,000 red blood cells and 480 white blood cells per cubic millimeter. The Pandy test was strongly positive. A blood count showed 85 per cent hemoglobin, 4,240,000 red cells and 12,000 white cells per cubic millimeter. The Wassermann test of the blood and of the spinal fluid was negative. Urinalysis gave negative results. Five days after admission the patient again passed into a semicomatose condition and from this into a stage of complete paralysis. A month later, at the time of discharge from the hospital, the only residual findings were complete paralysis of the left oculomotor nerve and increased tendon reflexes in the left extremities.

Gull and Schmidt separately have found that genuine aneurysms in the circle of Willis are revealed in from 0.5 to 1.5 per cent of all postmortem examinations. The relative frequency with which different vessels at the base of the brain are involved varies somewhat, depending on the number of cases in the series. Gowers reported the following distribution in a series of 154 cases: middle cerebral vessel, 44; basilar, 41; internal carotid, 23; anterior cerebral, 14; posterior communicating, 8; anterior communicating, 8; vertebral, 7; posterior cerebral, 6, and inferior cerebellar, 3.

There seems to be little preference for either side. In Fearnsides' series, which was the largest, in 24 cases the aneurysm occurred on the left side and in 26 on the right. In this same series, from the standpoint of sex, the condition was considerably more frequent in females than in males. Aneurysm has occurred at all periods of life, the youngest patient being a boy aged 6 years, who was admitted to the hospital with acute periostitis of the femur.

From an etiologic standpoint, Turnbull believed that these aneurysms may be divided into two groups: congenital and acquired. The factors concerned in their formation, especially of the latter form, are inflammation, degeneration, increased blood pressure and possibly trauma. In the cases of congenital aneurysm there

were almost universally other congenital vascular anomalies, such as coarctation of the aorta, atresia of the aorta, etc. In fact, Woltman and Shelden, reviewing 32 cases of congenital anomalies of the aorta, found that in 9.4 per cent there was an aneurysm at the circle of Willis.

The clinical manifestations. according to Symonds, may be divided into three groups: (1) those due to mechanical pressure on neighborhood structures, (2) those peculiar to the aneurysm itself—sudden leakage from the sac—and (3) those due to the disease which was the primary cause.

The site of the aneurysm is of primary importance in determining the focal signs. Aneurysms arising from the intracranial portion of the carotid artery, the proximal portions of the middle cerebral artery and the circle of Willis at the point of bifurcation of these vessels constitute the anterior group. Aneurysms involving these vessels produce a clinical picture which is remarkably constant. Owing to the higher incidence of aneurysms on the carotid portion of the circle of Willis and the constancy of the clinical pictures, aneurysms occurring in this location are diagnosed more frequently than those developing elsewhere. In the anterior group the focal signs and symptoms which may occur before rupture takes place differ in no way from those produced by other expanding lesions of the middle fossa. Pain localized in the supra-orbital region on the same side may exist for months or years before the focal signs appear. With increase in the size of the aneurysm other symptoms develop which are the result of direct pressure on contiguous structures: intermittent sharp shooting pains over the upper portion of the face, ptosis, diplopia and impairment of vision. Aneurysms of the basilar and vertebral arteries and their branches constitute the posterior group. The syndrome produced by this group is not as uniform as that produced by the anterior group. The seventh, eighth, ninth, tenth and twelfth cranial nerves may be involved by direct compression. The third nerve may be compressed by an aneurysm situated anteriorly at the bifurcation of the basilar artery. Perhaps the most common finding is weakness or paralysis of the extremities, caused by compression of the pyramidal tracts in the brain stem. This may take the form of recurrent attacks of hemiplegia on one side, or the hemiplegia may occur alternately, first on one side and then on the other. The pyramidal tracts may be compressed simultaneously, producing paraplegia. Bulbar symptoms, manifested chiefly by dysarthria and dysphagia, are not uncommon. Thrombosis of the basilar artery due to syphilitic endarteritis may produce a similar picture.

The characteristic symptoms of aneurysms begin when rupture occurs. Premonitory symptoms of an indefinite character may precede rupture for several days. The rupture of the aneurysm is usually manifested by a sudden apoplectic seizure, with loss of consciousness, vomiting and sometimes a convulsion. Death may occur at this time. If fatal hemorrhage does not occur, the patient gradually regains consciousness and complains of severe fronto-occipital headache, stiffness of the neck and perhaps pains in the extremities due to irritation of the meninges by the extravasation of blood into the subarachnoid space. The clinical picture resembles that of fulminating septic meningitis. Frequently the focal signs, notably palsy of the third nerve, appear at this time. The preexisting focal signs are increased owing to the formation of a clot around the aneurysm. The neurologic picture at this stage is of interest. Signs of meningeal irritation can be elicited—stiffness of the neck and the Brudzinski and Kernig signs. The meningeal signs. as a rule, are not so pronounced as those that one finds in cases of inflammation of the meninges due to bacterial invasion. In some cases with massive extravasation of blood into the subarachnoid space the signs of meningeal irritation may be minimal or absent. Fever and slight leukocytosis are almost constant findings. Hemiplegia, either transient or permanent, which occurs so frequently at the time of rupture of the aneurysm, may be due to several different causes. The aneurysm may rupture into the parenchyma of the brain and even into the ventricular system, producing considerable destruction of tissue. Again, intracerebral hemorrhages may occur in parts of the brain far removed from the site of the ruptured aneurysm.

In addition to the signs and symptoms resulting from the aneurysm and its rupture, there may be added the symptoms and signs of the underlying disease. The most uniform clinical picture of the associated disease is that produced by bacterial endocarditis: anemia, fever, leukocytosis, pains in the joints, cardiac murmurs, hematuria and other embolic phenomena. The sudden appearance of meningeal signs in the course of a subacute bacterial endocarditis should always make one suspicious of bleeding from a mycotic aneurysm. Focal signs of aneurysm in these cases are frequently absent, owing to the fact that mycotic aneurysms have a tendency to rupture before attaining a large size. Meningeal signs may also occur in this disease owing to bacterial invasion of the meninges, resulting in purulent meningitis. This, however, is an extremely rare complication.

From a diagnostic standpoint, Cushing, in discussing Symmonds' report, stated: "An aneurysm should always be considered in a differential diagnosis when an apoplectic attack or series of attacks of comparatively sudden onset is followed by symptoms pointing to the region of the internal carotid in its intracranial portion, namely, a unilateral oculomotor palsy with ptosis, and occipito-frontal pain with lowered sensitivity of the upper trigeminal skin field. Should there be in addition subhyaloid retinal hemorrhages, and should the cerebrospinal spaces be found to contain free blood (or possibly even xanthochromia in the intervals between periods of leakage) a diagnosis, as the author makes clear, is reasonably certain."

Treatment in these cases in the past has been merely palliative for the most part. Repeated lumbar puncture with the careful withdrawal of fluid, in order to relieve increased intracranial pressure, has been advised by several observers. This procedure, however, is not without danger. The disturbance of pressure relations within the cranium may result in increased bleeding from the aneurysm, and in some instances fatal hemorrhage has occurred. Surgical treatment, consisting of ligation of the internal carotid artery, has been used in a few cases in which an accurate diagnosis was possible. The value of this procedure is doubtful. Ligation of the internal carotid artery may produce hemiplegia, but if one remembers that this is a frequent complication of untreated aneurysm it is worthy of further trial in an attempt to avoid fatal rupture. SPAETH, Philadelphia.

THE BEARING OF RECENT WORK ON CERTAIN ASPECTS OF POLIOMYELITIS. J. PURDON MARTIN, Brit. M. J. **2**:1200 (Dec. 30) 1933.

This paper is in part a critical discussion of the views presented by Walshe before the Section of Neurology and Psychologic Medicine of the British Medical Association at the annual meeting in Dublin in 1933. Walshe denied the existence of a phase of systemic infection in cases of poliomyelitis and looked on the pathologic condition as being almost entirely confined to the nervous system. First, Martin thinks that the immunity which is widespread among the general population refutes, in part, the conclusions of Walshe. This immunity is acquired and does not depend merely on age; the immune bodies occur in the blood, and it seems unlikely that any strong reaction of this kind would occur in the blood if the infection or noxious substances were confined to the nervous system and did not enter the blood itself. Further evidence of general infection is to be found in the enlargement of lymph glands found post mortem in human beings, involving lymph follicles of the intestinal tract, Peyer's patches, the mesenteric lymph glands and the peripheral lymph glands, with hyperplasia in the thymus and in the malpighian corpuscles of the spleen, the tonsils, etc. Instances have occurred in which poliomyelitis following an injury has resulted in paralysis that has been maximal in the injured limb. This supports the idea that an infection circulating in the blood obtains entrance to a damaged nerve at the site of the injury.

It is generally agreed that invasion of the nervous system usually takes place directly from the nasopharynx. Several varieties of combinations are possible. General infection of the blood may result and the nervous system may not be attacked, or, if the nervous system is attacked, infection of the blood may occur at the same time or invasion of the blood stream may be somewhat earlier or

later than invasion of the nervous system. There may also be cases in which the infection invades the nervous system but not the blood stream. In the latter situation general infection probably occurs secondarily and late. The time relation between the onset of the general infection and the onset of the infection of the nervous system is likely to have an important influence on the course and outcome in any individual case. If, for example, the general infection precedes the infection of the nervous system, the earlier development of immune bodies in the blood will afford protection to the nervous system at an earlier stage of its invasion, but if, on the contrary, the general infection succeeds the infection of the nervous system or is actually secondary to it, widespread havoc is likely to be wrought in the nervous system before immunity is developed. The writer disagrees with Walshe on the interpretation of the so-called early nervous symptoms. Fever, headache, nausea, constipation or diarrhea, irritability or apathy and prostration form a complex of symptoms surely common enough with general infection. In a sense all symptoms are nervous, and it is a question whether in cases of poliomyelitis they are produced by actual infection of the nervous system or by the toxic action on the nervous system of a general infection. The degree of fever in cases of poliomyelitis is uncommon in cases of encephalitis but is common in general infections.

Textbooks describe six or seven clinical types of the disease conceived on an anatomic basis—spinal, brain stem, cerebral, cerebellar, meningeal and abortive. Martin finds no evidence for such a classification and makes a plea for the abandonment of the term polioencephalitis and the description of "cerebral" types of poliomyelitis.

Cases of poliomyelitis following injury support the conclusion that infection may in some cases be transmitted to the spinal cord along nerve paths from the bowel, the tonsil and other sources. Literature is cited to show that a number of cases of the bulbar form have followed tonsillectomy, indicating that the infection reached the bulb by way of the ninth and tenth cranial nerves.

In regard to immunotherapy, controlled observations have not established its merit, yet all theoretical knowledge is in support of the use of serum. It is not justifiable to conclude that because serum does not check the disease in a very susceptible monkey which has received a large intracerebral inoculation it cannot check it in a much less susceptible human subject who has received a much smaller dose. Since it is known that immunity is common among the general population, immune donors should not be difficult to find, and the testing of the blood of the usual professional blood donors against poliomyelitis should be undertaken. If serum is given it should be given intravenously, since it is doubtful whether direct absorption from the theca into the central nervous system is possible. Even more to be desired than a concentrated serum is a means of producing immunity. Martin quotes the work of Brebner of injecting a parent's blood to produce immunity; during this epidemic none of 1,300 children so treated contracted the infection. Another probable development in the future is a means of recognizing the susceptible members of the population, thus simplifying the problem of immunizing the community. He concludes that "our only hope of real protection against poliomyelitis lies in the attainment of a means of adequate and lasting immunity."

FERGUSON, Niagara Falls, N. Y.

CISTERNAL AND LUMBAR DRAINAGE IN THE TREATMENT OF COMA FROM ACUTE BARBITAL POISONING TOGETHER WITH OBSERVATIONS ON CHRONIC BARBITAL POISONING. JAMES PURVES-STEWART, Jahrb. f. Psychiat. u. Neurol. **51**:203, 1934.

Purves-Stewart points out that barbital derivatives are more powerful and potentially more dangerous than barbital itself, while the confusing claims for the various barbituric compounds, which are so assiduously placed on the market, enable a physician who has perhaps found barbital unsatisfactory to turn to one or other of the barbital derivatives until he learns, by bitter experience, that it is

only a similar drug under a new name. When barbital or one of its modifications is taken continuously for prolonged periods, even in ordinary therapeutic doses of from 32 to 65 cg., careful supervision is always necessary because the effects on the central nervous system do not always limit themselves to the desired hypnotic effect. Sometimes a cumulative and localized pathologic reaction may appear in other parts of the nervous system, such as the mesencephalon, the cerebellum and even the spinal cord, producing syndromes for which the patient may come under the care of the neurologist. In some cases the repeated use of such drugs may lead to the formation of definite drug addiction. Moreover, the barbital group of drugs has in recent years become increasingly popular for suicidal purposes.

To illustrate the toxic effect of moderate therapeutic doses of these drugs on the nervous system, Purves-Stewart describes in detail one case of poisoning due to barbital sodium in which the symptoms were referred to the posterolateral portion of the spinal cord, one case of poisoning due to a barbital derivative with amidopyrine in which a cerebellar syndrome resulted and one case of poisoning due to barbital sodium, a midbrain syndrome being produced.

In discussing acute barbital poisoning Purves-Stewart recalls that the physiologic effects of barbital and its allies include not only a specific hypnotic effect on the brain, for which they are ordinarily prescribed, but also an effect on the heart, lungs and kidneys. Larger doses, or in susceptible patients ordinary doses, cause acute and sometimes fatal coma. The most common symptoms of acute barbital poisoning are profound coma, with moderately contracted pupils, usually reacting to light, together with flaccidity of the limbs, loss of tendon reflexes, extensor plantar responses and loss of abdominal reflexes. The heart rate is rapid, cyanosis sets in and the blood pressure drops owing to the toxic effect on the myocardium. Blisters may appear on the skin, especially at sites of pressure. The drug is excreted rapidly into the urine and cerebrospinal fluid. In some cases suppression of urine may occur. There is generally terminal bronchopneumonia with pyrexia, and death occurs from cardiac failure.

The average minimum fatal dose is about 3.25 Gm., although 1 Gm. has been known to prove fatal. On the other hand, recovery has occurred under suitable treatment with doses as large as 13 Gm., and the author has observed a case of recovery after a single dose of 31 Gm. of barbituric compounds.

Treatment for acute barbital poisoning, as commonly carried out, includes prompt gastric lavage with warm water to remove any of the drug which may still remain in the stomach. About 550 cc. of hot coffee mixed with 120 cc. of a 10 per cent solution of dextrose and 30 cc. of castor oil are left in the stomach. The gastric lavage is repeated every four to six hours, two or three times. Colonic irrigation is also resorted to at once, and is repeated two or three times at intervals of twelve hours, followed by the rectal administration of dextrose. Warmth is applied to the body, and cardiac stimulants are given hypodermically every two hours, while strychnine hydrochloride in maximal doses (4 mg. at a time) and picrotoxin (2.5 mg.) are also given intensively. Inhalations of oxygen and carbon dioxide by nasal tube are helpful. The urine is withdrawn by catheter and, like the contents of the stomach, is preserved for chemical analysis.

These are the ordinary measures employed in cases of acute barbital poisoning. The most urgent indication, after washing out of the stomach, is to accelerate the removal of the drug from the nervous system and especially from the medullary centers which are continually bathed by the poison in high concentration. If, therefore, cerebrospinal fluid is withdrawn by lumbar puncture or better still by cisternal puncture, and if meanwhile no fresh barbital is being absorbed into the circulation, the new cerebrospinal fluid excreted by the choroid plexus will contain progressively diminishing quantities of the drug, and the prospects of recovery will be materially improved. The paper concludes with a detailed report of five cases of attempted suicide by means of unusually large doses of a barbital compound; in all the cases the foregoing method of treatment was used with complete recovery.

KESCHNER, New York.

THE CAUSES AND TREATMENT OF ARTHRITIS. CHARLES W. BUCKLEY, Brit. M. J. **1**:469 (March 17) 1934.

Buckley discusses only rheumatoid arthritis, which he divides into primary and secondary. In the former no focus of infection can be found; in the latter such a focus can be identified and dealt with as radically as possible, but wholesale extraction of foci may lower the resistance to such an extent that the disease gains a firm hold and the patient's condition is worse than before. Heredity is a factor in about 50 per cent of cases. The bodily characteristics are a slight, spare physique, the patient often being emotional, lacking in endurance and with poor circulation, cold extremities or liability to chilblains. This is probably the outcome of disturbances in the endocrine system, with sympathetic instability and defective assimilation of calcium. Buckley calls attention to the resemblance of this type of person to the one who is prone to tuberculous infection. The joints first affected are those which are most subjected to strain or which have been the seat of injury.

Opinions vary widely as to the form of streptococcus which is the probable cause of arthritis. Recent researches indicate that there are many culturally different strains which may be concerned in the etiology of rheumatic conditions. There is considerable evidence in support of the view that the articular and other lesions of rheumatic fever and also of acute infective or rheumatoid arthritis are due not to the actual presence of the infecting micro-organism itself in the affected tissues but to allergic effects. A polyarthritis alleged to be due to the organism of tuberculosis has been described, but Buckley has not been able to convince himself of the existence of this type of arthritis.

In regard to vaccine therapy, Buckley states that from his observations there have been more "cripples than cures" following the injudicious, uninstructed and often haphazard administration of a remedy which with care and skill has sometimes proved of great value. It seems illogical, when there is already an invasion of a living and toxin-producing microbe, to inject into the system further doses of the same microbe, even though dead. Yet there is clinical evidence that cure has at times followed this line of treatment, and thus, in the case of arthritis, there are enthusiastic advocates of vaccine therapy and others who condemn it with equal energy. It seems that vaccine of a specific type should be utilized only when an infective focus has been identified and eradicated. Autogenous vaccines may here be the most advantageous, but they must be started in small doses, their effects must be closely watched and the dosage and intervals must be regulated accordingly. Protein shock often gives good results, but perhaps oftener it fails and relapses occur. Stock vaccine may be used when a focus is still thought to exist, and in such cases if favorable results are likely to accrue there will soon be signs of this; if improvement is not quickly seen it is a doubtful policy to persevere with the vaccine or other protein shock. Intradermal vaccination has been tried. The author has obtained some positive and negative results with this form of therapy.

Treatment for arthritis with salts of gold has recently come into fashion. Several compounds have been tried, but chiefly sodium aurothiopropanol sulphonate. In Buckley's experiences a number of patients have shown promising results. Aurothioglucose has also been used. It is said to be less toxic and of higher therapeutic effect and is given by mouth. Good results are claimed for this method, although Buckley has had no personal experience with it. Iodine is widely employed and sometimes beneficially. Iodized poppy-seed oil 40 per cent, injected intramuscularly, may present some advantages over iodine in other forms. Iodide of iron with arsenic is a valuable tonic. Calcium is given extensively and should be used with vitamin D in the form of cod liver oil or its concentrate.

FERGUSON, Niagara Falls, N. Y.

TUMORS OF THE SYMPATHETIC NERVOUS SYSTEM. D. LEWIS and C. F. GESCHICKTER, Arch. Surg. **28**:16 (Jan.) 1934.

The records in a series of 103 cases of tumors of the sympathetic nervous system are presented in this report. Such tumors develop from cells which wander out from the neural crest during embryonic life. The undifferentiated cell may

give rise to the neuroblastoma, and as differentiation proceeds the more adult types of paraganglioma and ganglioneuroma may develop. The great variety of pathologic pictures of these tumors is due to differences in the stage of development of the cells, and the occurrence of various combinations of these types of tissues in the same tumor is an indication of their common origin.

The neuroblastoma is found at sites where the neuroblasts (sympathogonia) migrate from the neural crest to form the sympathetic ganglia and chromaffin tissue. In 33 of the 40 cases studied, the tumor was in the medulla of the suprarenal gland or in the sympathetic ganglia adjacent to the medulla. In the great majority the growth developed before the age of 15 years, almost one half being in children under 3 years of age. The clinical symptoms are protean, the most common being fever, recognition of an abdominal mass and anemia. Many of the symptoms result from pressure on the abdominal viscera. The clinical course is rapidly downward, with frequent metastases to the liver and bones. The tumor is usually a well encapsulated, solid or cystic, nodular growth varying from light yellow or gray to a dark reddish hue. It is composed of small cells with hyperchromatic nuclei and little cytoplasm, generally arranged in compact masses with frequent roset formation. Among these cells are larger round cells with vesicular nuclei and pear-shaped cells, and occasional masses of glia-like fibers.

The paraganglioma or chromaffin tumor is the most common of the tumors of the sympathetic nervous system, occurring 52 times in this series, and it is most frequently found in the medulla of the suprarenal gland, the carotid body, the submucosa of the appendix and small intestine, and the ganglia along the sympathetic nerves. It is usually solitary and benign and grows slowly. The paraganglioma of the carotid body is composed of well defined cell nests marked off by a delicate stroma, and not infrequently of numerous syncytial masses with a tendency to giant cell formation. Small lymphocytoid and spindle cells similar to those of the neuroblastoma are frequently encountered. The tumor occurs in adults and may be of long duration; its presence at the bifurcation of the carotid artery with an expansile pulsation may be suggestive of aneurysm. The paraganglioma or chromaffin tumor of the suprarenal medulla is generally a solitary, benign growth, occurring most frequently in the fifth decade of life. It may be associated with a great variety of clinical manifestations, such as vasomotor instability, hyperpiesis, Recklinghausen's disease, urinary or gastro-intestinal symptoms and Addison's disease. The tumor is usually well encapsulated, small or medium-sized and solid or cystic. The cells vary greatly in size, the cuboid or polyhedral forms of moderate size predominating, with a tendency toward syncytial formation.

Over 300 cases of paraganglioma or argentaffin tumor of the appendix have been reported. Paraganglioma of the gastro-intestinal tract occurs in adults and usually has a slow, benign course. About 20 per cent of these tumors undergo malignant change. Symptoms of appendicitis or partial intestinal obstruction may occur.

The authors' addition of 8 cases of ganglioneuroma brings the number of reported cases of this tumor to 111. This type of tumor is usually benign and solitary but may be multiple and malignant; it appears at ages varying from 4 to 45 years. It may be found anywhere in the central or peripheral nervous system. The clinical course is usually slow and symptoms are due to the gradually increasing pressure of the tumor on surrounding structures.

SPERLING, Philadelphia.

THE MENACE OF HEREDITARY BLINDNESS. J. MYLES BICKERTON, Brit. M. J. **1**:93 (Jan. 20) 1934.

Bickerton remarks that the "total world figures relating to blindness must be of staggering dimensions," with evidence that it is on the increase. Blindness in the more active years of life is largely avoidable, while much of it is due either to definitely dysgenic birth or to the unrestricted production of children in poor or in bad circumstances. For example, trachoma, which accounts for 2 per cent of

cases of blindness, does not occur in clean households. Purulent conjunctivitis, which accounts for another 2 per cent, rarely occurs in clean households. Ophthalmia neonatorum, which accounts for 5 per cent, can be avoided entirely by proper preventive measures at birth. Accidents, which account for 5 per cent, frequently occur in families in which it is impossible to give the children proper care and protection. Fifteen per cent of cases of blindness are due to syphilis, and it is probable that 10 of this 15 per cent are due to congenital syphilis. This can be entirely corrected by proper treatment of the pregnant mother, by the prevention of conception or by abortion. Of greatest importance and interest is the incidence of the types of blindness which are strictly hereditary: due to congenital defects, 6 per cent; due to glaucoma, 1 per cent; due to extreme myopia, 14 per cent; due to senile cataract, 1 per cent; other types, 2 per cent—a total of 24 per cent or practically one quarter of all forms of blindness. Albinism occurs to the extent of 1 in 10,000. Practically all albinos are below the average in health and vitality; many are aments, and all, as a direct result of the albinism, have photophobia because the eyes lack the pigment to protect the sensitive retina. Often they suffer from nystagmus or myopia. Thirty per cent of the cases of blindness are due to consanguineous marriage. Myopia tends eventually to cause blindness or very defective vision. Myopia tends to be recessive, and some observers have found that in 100 families with one myopic parent there were 200 myopic children and 250 nonmyopic children; while in 91 families with neither parent myopic, only 100 had myopia and 300 did not have it. Some authorities state that nearly 4 per cent of all cases of blindness are due to hereditarily determined atrophy of the retina (retinitis pigmentosa). Atrophy of the optic nerve and optic neuritis frequently cause blindness, and the hereditary variety is well recognized. In 1,000 pedigrees available for study, 85 per cent of the persons with this condition were males. The malady has been traced through six generations in 1 case. Absence of the iris (aniridia) is also a hereditary affliction. One man blind as a result of this condition procreated 13 children, all similarly affected; 61 of 63 grandchildren were affected and 39 of 42 great-grandchildren. Congenital cataracts and senile cataracts account for a large number of cases of blindness. According to some authorities, 13 per cent of the pupils in schools for the blind are blind because of cataract. Congenital displacement of the lens has been traced as a dominant through six generations. In glaucoma the hereditary factor is not always marked, though congenital glaucoma does occur. Blue sclerotics, frequently associated with fragilitas ossium and otosclerosis, are more common in the female and are transmitted by the female. A malignant gliomatous growth of the nerve elements of the eye occurs in infants and shows a strong hereditary tendency. In the group of conditions designated as maculocerebral degenerations is included amaurotic family idiocy. This condition fortunately is rare. Night blindness is also transmitted both as a dominant and as a recessive sex-linked hereditary defect.

Some of the possible remedies suggested by Bickerton to prevent and control blindness are: (1) constructive birth control to avoid overcrowding and poverty; (2) sterilization of mental defectives and possibly others; (3) review of the obsolete and ancient abortion laws; (4) euthanasia for infants with gross defects, to be available for parents who wish to make use of it; (5) the performance of Wassermann tests during or before pregnancy.

FERGUSON, Niagara Falls, N. Y.

STUDY OF THE MODIFICATIONS OF THE VISUAL FIELD IN SYNDROMES OF HYPERTHYROIDISM AND EXOPHTHALMIC GOITER. P. L. DROUET, P. JEANDELIZE and A. GAULT, Ann. d'ocul. **171**:465 (June) 1934.

In recent studies of hyperthyroidism, Labbé, his associates and Dautrebande emphasized the clinical aspect and the necessity of studying basal metabolism, which is always high in cases of hyperthyroidism. This rise of basal metabolism differentiates exophthalmic goiter from "parabasedowian" disease (so-called by Labbé). This disease is characterized by a clinical picture in which certain cardinal signs

of exophthalmic goiter (exophthalmos, goiter, tremors and tachycardia) are present, but basal metabolism is normal. Certain authors have classified this syndrome with latent exophthalmic goiter, tachycardiac neurosis, pseudohyperthyroidal neurosis (Maranon), thyroid instability, etc. Labbé expressed the belief that the symptomatology of parabasedowian disease is controlled by the sympathetic nervous system, excluding the thyroid gland.

Ocular symptoms are common in cases of exophthalmic goiter and in parabasedowian disease. They vary in intensity and frequency and are encountered in practically all cases. The most important ocular signs are exophthalmos, Graefe's sign, Stellwag's sign, Möbius' sign, dilatation of the pupils, nystagmus and epiphora.

The authors emphasize the importance of contraction of the bitemporal visual field. This sign appears important because of its possible significance in confirming neuro-endocrine syndromes. The detection of contraction of the visual field is important in patients who show a pathologic endocrine condition. In this way the pituitary gland is apparently associated with hyperthyroidism, and hyperactivity is further suggested when bitemporal contraction of the fields is associated with hypophyseal elements in the blood or urine.

This ocular sign should be searched for whenever functional disturbance of the gland is suspected. If the attempt is made to judge by the important and numerous characteristics which the hypophysis possesses, without doubt the results of the examination will be unsuccessful. Contraction of the bitemporal visual field of hypophyseal origin is not and should not be considered unusual except in cases of tumor. From these observations the authors state that in cases of exophthalmic goiter hyperthyroidism and hyperpituitarism are present but that in the parabasedowian syndrome there is only hyperpituitarism.

In conclusion, the authors emphasize the usefulness and necessity of a systematic study of the visual field in clinical cases in which the hypophysis may have an important rôle. The field of this examination should be enlarged, for this examination permits one in many of these cases to observe the part which the pituitary gland plays in certain syndromes and also clarifies the pathogenesis.

For several years Drouet, Jeandelize and Gault have assisted in studying certain hypophyseal functions. These may be determined by a certain number of biologic reactions studied apart from the serum or the urine. The facts on which this paper is based are associated with these humoral reactions; although these methods permit only the determination of hyperactivity of the hypophysis, they demonstrate progress, as they show the intervention of this gland in pathologic conditions in which its rôle has seemed unimportant or hypothetic. BERENS, New York.

GLIOMAS OF THE CORPUS CALLOSUM. G. ARMITAGE and R. MEAGHER, Ztschr. f. d. ges. Neurol. u. Psychiat. **146**:454 (June) 1933.

Armitage and Meagher report twelve cases of glioma of the corpus callosum among two thousand verified cases of tumor of the brain in Cushing's series. In no instance was the correct diagnosis made by neurologic examination alone. "Nevertheless, when these cases are collected as a composite group, they show a fairly definite syndrome characterized by a rapidly advancing lethargic psychosis and generalized weakness, often coupled with astasia."

There were eleven cases in males and one in a female. The average age was 49 years. All the tumors were gliomas; eight were glioblastoma multiforme and four were astrocytomas. The survival period in both groups from the first onset of symptoms was nineteen months. None of the tumors was confined to the corpus callosum. Headache and choked disk were present in eleven cases. Psychic disturbances were present in all twelve cases. This coincides with the investigations of others, Muinigazzini particularly stressing the early appearance of mental signs. In nine of the twelve cases mental changes occurred early in the disease. Usually the first mental symptom observed in callosal tumors is a loss of spontaneity in emotion, thought and activity. This passes into apathy, usually accom-

panied by drowsiness, failing memory, particularly for recent events, and mild deterioration, advancing to deeper torpor, coma and death. The progress is usually rapidly downward. Eight patients in the series showed this lack of spontaneity, apathy and stupor. Two showed manic changes. There are no pathognomonic mental states in cases of callosal tumor.

Spastic paraplegia was present in only one case, despite Schuster's assertion that psychic disturbances and bilateral signs referable to the motor tract were the important features in cases of these tumors. In ten there was subjective loss of strength, which could often not be confirmed by examination. The weakness usually includes all four extremities equally. The deep reflexes were increased in eight cases bilaterally, with more marked increase on one side in five. In one case there was diplegia and in three cases hemiplegia. Only two patients could stand upright and walk normally. Eight patients had marked irregularities in station and gait. The station was usually with a wide base, and four patients showed a tendency to retropulsion. The gait was unsteady and ataxic. In six cases there were convulsions; three were of the jacksonian type. Nine patients were incontinent. Only one patient, who had hemiplegia, showed any signs referable to the cranial nerves; this patient had central facial palsy. There were no sensory disturbances. None of the patients showed apraxia.

There is no specific symptom which is pathognomonic of callosal tumor. However, the combination of progressive mental deterioration, bilateral motor disability and rapid progress of the disease are extremely suggestive. Armitage and Meagher state that accurate diagnosis without ventriculography is almost impossible.

ALPERS, Philadelphia.

MONOCULAR DOUBLE IMAGES: THEIR ORIGIN AND SIGNIFICANCE FOR THE THEORY OF THE FUNCTION OF THE NERVOUS SYSTEM. KURT GOLDSTEIN, Jahrb. f. Psychiat. u. Neurol. **51**:16, 1934.

Goldstein describes in detail the cases of two patients with organic disease of the brain associated with monocular diplopia. He summarizes his conclusions as follows: 1. Monocular diplopia is not always hysterical. In cases in which it is organic, double images occur when there is hypofunction of the optic apparatus, and only when the hypofunctioning portions of the retina are stimulated. 2. Diminution of vision may be due to damage of the optic sector (central amblyopia) or to interference with vision on account of the abnormal "tonic pull" of the affected eye. 3. With the appearance of the double image there occurs a displacement of the principal image; the displacement is in the direction which stimulates areas of the optic apparatus possessing better visual function; it may be in the direction of parts of the retina nearer to the macula, or it may be in the direction which overcomes the "tonic pull" so that the "visual situation" is generally improved. Improvement in vision runs parallel to the appearance of double images and to the displacement of the principal image. 4. Factors causing bad vision enhance the appearance of double images and vice versa. 5. Double images as well as displacement and improvement of vision occur also when the macula is stimulated, but only when the eye is brought into a definite position.

Goldstein offers the following theoretical explanation for monocular diplopia: 1. Double images are produced by abnormal irradiation of the stimulus, which gives rise at first to a "spreading" of the image to the side of the irradiation of the stimulus and then to two images varying in distinctness and clearness (as to light). The image which is less clear corresponds to the site of the original stimulus, whereas the displaced principal image corresponds to the site of the irradiation of the stimulus. 2. The irradiation of the stimulus serves during defective vision to raise the threshold of the stimulus. The tendency to attain as much vision as possible is the starting-point for the irradiation of the stimulus, which leads eventually to displacement and thus to the formation of double images. 3. The organism accepts the disturbing effect of double vision as a compromise to

obtain as much vision as possible, because for the total body function it is less inconvenient to have double vision than poor vision. 4. The "visual value" of a part of the retina as well as of the macula also depends on the position of the eyes.

KESCHNER, New York.

ACETARSONE IN THE TREATMENT OF NEUROSYPHILIS. LEON H. GRIGGS and JAY F. SCHAMBERG, Arch. Dermat. & Syph. **29**:645 (May) 1934.

Acetarsone was shown to be of definite therapeutic value in seventeen cases of neurosyphilis studied by the authors. Six of the cases are reported in detail. Patients with atrophy of the optic nerve were not given this form of treatment.

1. Asymptomatic neurosyphilis: The Wassermann reaction of the blood was positive before and negative after the treatment. Eighteen grams of acetarsone was used in each course. The colloidal gold curve of the spinal fluid improved from 4445321000 to 0000000000.

2. Early dementia paralytica: A total of 19 Gm. of acetarsone was administered. The colloidal gold curve improved slightly; the reactions to the Wassermann and Kahn tests were unchanged; the cell count was reduced from 33 to 2.

3. Asymptomatic neurosyphilis: A total of 12.5 Gm. of acetarsone was administered. The serologic reactions improved from strongly to weakly positive.

4. Tabes dorsalis: A total of 11 Gm. of acetarsone was administered. The reactions of the blood and spinal fluid were negative both before and after the treatment.

5. Tabes dorsalis: A total of 16.5 Gm. of acetarsone was administered. The Wassermann reaction was reduced from strongly to weakly positvie.

6. Asymptomatic neurosyphilis: A total of 13.5 Gm. of acetarsone was administered. The Kolmer reaction was reduced from positive to negative.

Dimness of vision developed in one patient; vision, however, became normal after cessation of treatment. Two patients complained of diarrhea, which was controlled by restricting the diet. Most of the patients obtained relief from pains and many gained weight. The authors consider that acetarsone is worthy of more extensive use in the treatment of neurosyphilis.

DAVIDSON, Newark, N. J.

THE INNERVATION OF THE SMALL INTESTINE. OTTORINO ROSSI, Jahrb. f. Psychiat. u. Neurol. **51**:214, 1934.

Rossi studied the nerve supply of the small intestine, employing the Golgi impregnation method and variations of the Cajal silver nitrate method. His conclusions are: 1. The small intestine contains nerve fibers which reach the intestinal wall through a small bundle of nerves to enter finally the plexus of Meissner. 2. Other nerve fibers which reach the intestine in the same manner run directly into the intestinal villi and epithelium. 3. Nerve fibers from Auerbach's plexus reach Meissner's plexus. 4. Delicate varicose nerve fibrils from Auerbach's plexus extend into the submucosa, intestinal villi and intestinal epithelium. 5. An attempt to ascertain the origin of fibers described under 3 and 4 was unsuccessful. 6. Some of the nerve cells of Auerbach's plexus which can be regarded as Cajal's cells (type 2) have a long prolongation possessing morphologic characteristics of an axis-cylinder. 7. In the muscular layer there may be observed: (*a*) small nodules of sympathetic nerve cells resembling those of Auerbach's plexus, which in addition to other prolongations also have one that resembles morphologically an axis-cylinder; (*b*) individual sympathetic nerve cells, and (*c*) small nerve cells varying in structure, which cannot be disregarded in a discussion of the so-called interstitial cells. 8. The ganglion cells in Meissner's plexus show, in addition to other dendrites, a long prolongation resembling morphologically an axis-cylinder. In this plexus there are to be seen nerve cells which can be readily distinguished by

the peripheral direction which their long prolongation takes. 9. The submucosa contains not only cells of the interstitial type but also genuine sympathetic ganglion cells resembling those in Meissner's plexus. 10. There are observed in the various layers of the intestine nerve fiber formations resembling so-called nerve endings.

KESCHNER, New York.

EFFECT OF TRYPARSAMIDE ON THE EYE. N. K. LAZAR, Arch. Ophth. **11**:240 (Feb.) 1934.

There have been many reports concerning the effect of tryparsamide on the body since Jacobs and Heidleberger first produced it and since its introduction into the therapy of neurosyphilis. Few, however, are based on an experimental histopathologic study. Lazar made such a study and reported a case of blindness that was supposed to have been the result of treatment with tryparsamide. In addition, thirty-two cases of syphilis of the central nervous system in which this drug had been used were observed and are reported, with a review of the literature; opinions are presented which in some instances are contradictory.

Lazar draws the following conclusions relative to tryparsamide and its relationship to syphilis and damage it may do in the eye: 1. Experimentally, one cannot demonstrate any histopathologic changes in the eyes, optic nerve, chiasm or brain of lower animals or man which can with certainty be attributed to tryparsamide. 2. The definite loss of vision so soon after the injection of tryparsamide leaves no doubt of a definite toxic effect of the drug on the visual apparatus of certain patients. 3. Serious and even permanent damage may occur to a previously normal visual apparatus. 4. The tragic results which do occur from time to time illustrate the danger of giving the drug to persons showing evidence of atrophy of the optic nerve. 5. Persons to be treated with tryparsamide should be given a full ophthalmic examination, including examination of the visual fields before treatment is instituted, and after the first three to six doses the fields should be examined before another treatment is given. Atrophy of the optic nerve or constricted fields are positive contraindications to the injection of the drug.

SPAETH, Philadelphia.

THE ANALYSIS OF PSYCHOTICS. PAUL FEDERN, Internat. J. Psycho-Analysis **15**:209 (April-July) 1934.

Federn stresses that environment has a great deal to do in modifying the course of a psychosis and especially the effectiveness of therapy. In no case has he ever succeeded when there was no cooperation on the part of the family. An important addition should be psychoanalytic training of nurses and attendants, as they have a great deal to do with the patient. Transference is much more important in the psychotic patient than in the neurotic patient. A psychotic patient is accessible to psychoanalysis only if he is still capable of transference, if he has a certain amount of insight into the abnormal state and if he has definite orientation toward reality. The main thing is not to increase regression. One must be content with the material which the patient brings up and not attempt to force the uncovering of deeper strata by means of free association or by withholding countertransference. One must constantly attempt to bring the schizophrenic patient back to reality, and this requires considerable modification of the usual psychoanalytic technic. The more normal the patient's environment is, the easier it will be for him to control his odd ideas. The onset of the disease can easily be traced to libidinal disappointments or to the intensification of the libido during various biologic tides, as, for example, in puberty. The aim of therapy is to counteract the tendency to flight, which carries the patient away from objects and from reality. Catatonic rages give a good idea of what the various factors are which caused the patient's special behavior. There must be a good deal of respect for the patient's personality on account of the extreme sensitiveness. One can only hope for a social recovery, and restoration of the ego structure is as far as one can go.

KASANIN, Howard, R. I.

SUDDEN RIGHT HEMIPLEGIA AND DYSARTHRIA OCCURRING IN A YOUNG MALE NEGRO SOME FIVE WEEKS AFTER CESSATION OF BRIEF ARSENICAL THERAPY; EVIDENCES OF SYPHILITIC MENINGITIS AND ARTERIAL OCCLUSION BUT NOT OF NEURO-RADICULITIS; DISCUSSION OF DIAGNOSIS AND THERAPY. LEWELLYS F. BARKER, Am. J. Syph. **17**:321 (July) 1933.

Neurorecurrences are due to inadequate rather than to excessive arsenical treatment. Brief treatment destroys extraneural foci, thus preventing the response of the tissues and the development of immune substances. Proper intensive treatment by the combined method will destroy the spirochetes, both intraneural and extraneural, and will prevent the development of neurorecurrences. Barker cites an illustrative case. A man, aged 22, after having received six doses of neoarsphenamine and six doses of arsphenamine, abandoned treatment. Five weeks later he experienced numbness of the right arm, and on the following day a right hemiplegia developed with apoplectic suddenness. The face was included in the paralytic process, which was of a spastic type. The Wassermann reaction of the blood was negative, but that of the spinal fluid was four plus. The colloidal gold curve was 5555321000. Arterial occlusion (lenticulostriate) was probably the cause. Under arsphenamine, bismuth and iodide therapy the patient showed definite improvement within a few days. The medication was accompanied by spinal drainage, which was performed every ten days or two weeks. The importance of early and intensive antisyphilitic treatment is illustrated and stressed.

DAVIDSON, Newark, N. J.

THE NATURE OF THE THERAPEUTIC ACTION OF PSYCHO-ANALYSIS. JAMES STRACHEY, Internat. J. Psycho-Analysis **15**:127 (April-July) 1934.

Strachey summarizes his extensive paper as follows: "(1) The final result of psycho-analytic therapy is to enable the neurotic patient's whole mental organization, which is held in check at an infantile stage of development, to continue its progress towards a normal adult state.

"(2) The principal affective alteration consists in a profound qualitative modification of the patient's super-ego, from which the other alterations follow in the main automatically.

"(3) This modification of the patient's super-ego is brought about in a series of innumerable small steps by the agency of mutative interpretations, which are affected by the analyst in virtue of his position as object of the patient's id-impulses and as auxiliary super-ego.

"(4) The fact that the mutative interpretation is the ultimate operative factor in the therapeutic action of psycho-analysis does not imply the exclusion of many other procedures (such as suggestion, reassurance, abreaction, etc.) as elements in the treatment of any particular patient."

This article is by far the most lucid and coherent account of the actual technic of psychoanalytic therapy and tells frankly what the analyst does with the patient. Unfortunately, there is dragged in a good deal of recent metapsychology of Melanie Klein which obscures rather than clarifies the author's excellent presentation.

KASANIN, Howard, R. I.

EPILEPSY AND CONVULSIONS IN DIABETES. WILLIAM R. JORDAN, Arch. Int. Med. **52**:664 (Nov.) 1933.

Although there are frequent references in the literature to the rare coexistence of epilepsy and diabetes, an analysis of Joslin's series of five thousand diabetic patients shows this opinion to be in error. Jordan found nineteen cases of undoubted epilepsy and three of probable grand mal in these patients. On the basis of the general incidence of these diseases one can compute the theoretical incidence of epilepsy to be 1.7 per thousand diabetic persons. In this series the incidence is 2.3—actually greater than expectancy. Furthermore, when one remembers that in most cases the onset of diabetes is after the age of 40, while

epilepsy is rarely acquired after that age, the falseness of the concept of the rarity of the coexistence of these diseases becomes more striking. Of course, in making a diagnosis of epilepsy in a diabetic person one must be careful to exclude hypoglycemic and arteriosclerotic convulsions. An additional error is introduced in cases in which alkaline therapy is used in diabetes, for the association with alkalosis and paroxysmal disorders (such as tetany) may lead to a false diagnosis of grand mal. If the diabetes is permitted to progress without control, the acidosis will probably eliminate the seizures, but this therapy is obviously undesirable. Jordan is reluctant to use dehydration or a ketogenic diet because of the dangers of severe and possibly fatal states of acidosis. Treatment for epilepsy, therefore, is limited largely to bromides or phenobarbital.

DAVIDSON, Newark, N. J.

EXTRACT OF THE POSTERIOR PITUITARY LOBE AND ITS ACTION ON THE BLOOD CHLORIDE. P. L. DROUET, VÉRAIN and L. COLLESSON, Rev. franç. d'endocrinol. **12**:1 (Feb.) 1934.

This article is a report of experimental work dealing with the problem of chloride metabolism and the action of the extract of the posterior lobe of the pituitary on gastric acidity. Injections of this extract into persons with an intact renal system and intact hypophysis caused a decrease in the total chlorine of the cells, not affecting to any appreciable degree the chlorine in the plasma. There was a uniform increase in the chloride content of the urine; it also produced a decrease in the gastric hydrochloric acid. In cases of lesions in the hypophyseal region the posterior lobe pituitary extract produced the opposite effect. The authors, therefore, conclude that there are centers in the hypophysis and in the floor of the third ventricle which regulate chloride metabolism.

NOTKIN, Poughkeepsie, N. Y.

POSTURAL RELATIONS OF THE FRONTAL AND MOTOR CORTEX OF THE DOG. CLINTON M. WOOLSEY, Brain **56**:353 (Dec.) 1933.

Differential ablations of the motor and frontal cortex, controlled histologically and by electrical stimulation, were performed on thirty-two dogs. It was found that the excitable area extended beyond the distribution of the Betz cells, overlapping the sensory granular cortex. Lesions anterior to the electrically excitable area were not associated with clinical manifestations; symptoms appeared when the excitable area was involved and were maximal when the entire excitable area was ablated. The contralateral changes were extensor rigidity, hypertonicity of the musculature of the trunk, uncorrected postures of the extremities, failure of placing and hopping reactions, hyperactive tendon reflexes and decreased sensory responses. It is suggested that the rigidity appears because the reflex mechanisms of this level have been abolished and that the experimental "motor" lesions are a combination of sensory and motor elements.

THE PERSONALITY TYPE OF PATIENTS WITH ARTERIOLAR ESSENTIAL HYPERTENSION. DAVID AYMAN, Am. J. M. Sc. **186**:213 (Aug.) 1933.

The lack of adequate studies of personality types is stressed. The procedure reported was based on responses to the same specifically worded direct questions in regard to personality. The results showed that patients with hypertension tend to be emotionally hyperactive, physically hyperactive or both. They tend to be highstrung and unusually sensitive, to blush easily, to be unusually serious and to eat and talk rapidly. It is suggested that the hypertensive personality is of lifelong duration. The differentiation of the hypertensive personality from the psychoneurotic, neurasthenic and manic-depressive types is discussed. The etiology remains unsettled. The recognition of the hypertensive personality may be of definite aid in the diagnosis of arteriolar (essential) hypertension. Therapy should be directed toward modifying the personality either by education, by sedation or by both.

ALLERGIC MIGRAINE: II. ANALYSIS OF A FOLLOW-UP AFTER FIVE YEARS. WARREN T. VAUGHAN, Am. J. M. Sc. **185**:821 (June) 1933.

Of sixty-three patients, twenty-five reported excellent results, seven good and eleven fair, and twenty had no relief. In 70 per cent evidence of an allergic factor was found. Nausea was present in 85.2, vomiting in 60.4 and ocular symptoms in 39.9 per cent. A family history of migraine was obtained in 83 per cent of the patients who were relieved and in 69 per cent of those who were not relieved. More than 50 per cent presented other allergic symptoms. Age and duration are not significant factors. Interpretation of the reaction of the skin is probably the most important factor in obtaining results. The foods most frequently causing migraine were wheat, milk, peanuts, chocolate, pork, peas, beans, onions, eggs and bananas. In conclusion the author presents a program for a systematic analysis in each case of migraine from the point of view of allergy.

OBSERVATIONS ON THE PRODUCTION OF PAIN AND FATIGUE IN MUSCULAR ISCHEMIA AND THEIR RELATIONSHIP IN ANGINA PECTORIS. LOUIS B. LAPLACE and MARTIN P. CRANE, Am. J. M. Sc. **187**:264 (Feb.) 1934.

Pain arising in the human limb during repeated muscular contractions in the presence of varying degrees of ischemia was observed in thirty-six subjects. No relationship was apparent between the onset of pain and the duration of exercise, the rapidity of development of pain or its ultimate intensity. The arrest of the circulation favored the development of both pain and fatigue, but they were not affected to the same extent by different degrees of ischemia or by variations in the type of work. Subjects exhibiting neurotic tendencies did not show marked disposition to the development of muscular pain during the experiments. It is improbable that nervous sensitivity is a significant factor in the production of angina pectoris.

FORMATION OF A HEMATOPOIETIC SUBSTANCE IN CONCENTRATED HUMAN GASTRIC JUICE. PAUL J. FOUTS, O. M. HELMER and L. D. ZERFAS, Am. J. M. Sc. **187**:36 (Jan.) 1934.

Through a progressive series of experiments it was found that the "active principle" in the gastric juice could not be separated from the known enzymes, pepsin and rennin, by the process of ultrafiltration except after concentration by vacuum distillation. Fresh human gastric juice after concentration by ultrafiltration was inactive. When gastric juice that had been stored in the icebox for two months was concentrated by ultrafiltration and when fresh gastric juice was first concentrated by vacuum distillation, active preparations were obtained. The possible mechanisms involved in the change of the gastric juice are discussed. It is suggested that the hematopoietic substance must be formed by the action of the intrinsic factor on an extrinsic factor or by the production of a substance irritating or toxic to the hematopoietic substance.

MAINTENANCE OF NORMAL BLOOD IN PERNICIOUS ANEMIA BY MEANS OF INTRAMUSCULAR INJECTIONS OF A SOLUTION OF LIVER EXTRACT. WILLIAM P. MURPHY, Am. J. M. Sc. **186**:271 (Aug.) 1933.

It is pointed out that maintaining an essentially normal condition of the blood is as important as treating a patient whose blood is already in a state of relapse. Under the course of treatment, the patient remained in better general health and improvement in nervous symptoms has been unusually striking. The level of the red blood cells should remain preferably at or above 5,000,000 cells per cubic millimeter: intramuscular injections probably favor better absorption and utilization of the active substance. Reactions to this type of treatment have been

negligible. From eighty-one instances it was determined that an intramuscular injection of the amount of solution derived from 100 Gm. of liver (3 cc.), at intervals varying from one to six weeks, has the desired maintenance effect.

ASSOCIATION OF PITUITARY TUMOR AND PEPTIC ULCER. BERNARD I. COMROE, Am. J. M. Sc. **186**:568 (Oct.) 1933.

A review of the literature failed to reveal a single case in which a diagnosis of tumor of the pituitary gland associated with peptic ulcer was made during life. A white girl, aged 19, had a penetrating duodenal ulcer, a pituitary adenoma (infantile uterus and amenorrhea) and a simple nontoxic goiter. A white man, aged 57, had a Rathke's pouch tumor, gastric ulcer and possible Addison's disease. It is suggested that an excessive production of pituitary, the hypothetic autonomin, may have been instrumental in causing the ulcerative processes in the gastrointestinal tract. Treatment in the early stages of certain cases of peptic ulcer by subcutaneous injections of solution of pituitary may be worthy of trial. The possibility of the coincidental occurrence of the two diseases as unrelated events might have been considered.

ON THE CONNECTIONS OF THE MEDIAL CELL GROUPS OF THE THALAMUS. W. E. LE GROS CLARK and R. H. BOGGON, Brain **56**:83 (March) 1933.

An experimental investigation of the fiber connections of the medially situated nuclei of the thalamus is reported. Electrolytic lesions were produced in the thalamus of the cat, and the course of the degenerated fibers was studied by the Marchi method. The nucleus dorsomedialis sends fibers to the periventricular system and cortical projection fibers to the prefrontal region of the cortex. The nucleus medialis ventralis has no direct cortical connection. Lesions of the midline nuclei produced degeneration limited to the commissural fibers and the periventricular fibers. In lower mammals, the prefrontal cortex and the cortex of the gyrus cinguli must be included among the thalamocortical projection zones.

SUBDURAL FALSE MEMBRANE OR HAEMATOMA (PACHYMENINGITIS INTERNA HAEMORRHAGICA) IN CARCINOMATOSIS AND SARCOMATOSIS OF THE DURA MATER. DOROTHY S. RUSSELL AND HUGH CAIRNS, Brain **57**:32 (March) 1934.

The association of pachymeningitis interna haemorrhagica with malignant disease of the dura has not been widely recognized and has more pathologic than clinical significance. Four cases are described. The subdural hematoma was formed in the areolar layer of the dura and was the result of mechanical interference with the circulation by permeation of the veins and the capillaries with growth. Hemorrhage was the most important factor. Histologically, the subdural membrane was similar to idiopathic pachymeningitis haemorrhagica interna and traumatic subdural hematoma.

ACCIDENTAL HYPODERMIC TRANSMISSION OF MALARIA IN DRUG ADDICTS. L. MCKENDREE EATON and SAMUEL M. FEINBERG, Am. J. M. Sc. **186**:679 (Nov.) 1933.

From the study of 197 histories of patients, observations are gathered to corroborate Biggam's statement as to the accidental hypodermic transmission of malaria among heroin addicts. Addicts did not give the usual history of onset or recent exposure in a recognized malarial district. The onset of malaria in drug addicts showed no seasonal increase, as in natural infection, but was found to occur as one would predict if the infection were accidental and artificial. In 1932, 35 per cent of all men with malaria admitted to Cook County Hospital were addicts, taking the drug hypodermically.

MICHAELS, Boston.

Society Transactions

PHILADELPHIA NEUROLOGICAL SOCIETY

May 25, 1934

D. M. McCarthy, M.D., *President, in the Chair*

Anomia: Report of a Case. Dr. William Drayton.

This article will be published in full elsewhere.

Diathermy of the Brain for Patients with Hemiplegia. Dr. A. A. Martucci.

This is a preliminary report on the work being done on some patients with hemiplegia treated in the department of physical medicine at the Episcopal Hospital. After procuring the usual results following months of treatment of a number of these patients who were referred to the department for the production of passive and active movements, massage, reeducation of the muscles and baking and stretching of the affected limbs, my associates and I thought of the possibility of instituting diathermy at the point of origin.

With the aid of Dr. Hadden, the literature was scanned for help. The effect of diathermy directly on the brain has not been mentioned in the literature. The attitude was that diathermy to the brain was generally regarded as risky; nevertheless the success with which diathermy had been used in other conditions induced us to try it on the brain of patients with hemiplegia.

Experiments performed by Dr. McFee, of the Walter Reed Hospital, proved rather definitely that heat produced within the tissues by diathermy is of a conversive type and that such heat is evenly distributed throughout the tissues, the area of greatest heat being at the site of the smaller electrode. I have treated children with gonococcic vaginitis by placing electrodes along the upper part of the sacrum, above the symphysis pubis, and an active electrode in the vagina. Twenty minutes after treatment the vaginal thermometer registered a local rise in temperature to 112 F. This, of course, was due entirely to the concentration of the current in the vaginal canal by means of the vaginal electrode. If such conditions are possible, the current being regulated at will and placed at the site almost with precision, is it not fair to assume that electrodes placed on the head of the patient with hemiplegia in the proper position can be used to advantage in the treatment?

At the Hospital of the Protestant Episcopal Church good results have been obtained in 4 cases. This paper is presented with the hope that further research will be carried out. As yet we are not fully conversant with the indications and contraindications for diathermy.

Report of Cases.—Case 1.—A. W., aged 51, had had right hemiplegia for one year. He could not use the right arm or right leg without help and had loss of speech. Diathermy was applied to the brain with a small electrode over the left frontal area and a larger electrode below the occipital protuberance. At the first treatment, on March 9, 1934, twenty minutes of diathermy was given, a dosage of 750 milliamperes being used. Following this the patient showed no untoward effects. Three days later thirty minutes of diathermy was given, with no untoward effects. The son stated that his father was less nervous and that for the first time in one year he had been able to sleep through the night. Following the third treatment the patient spoke a word. He was treated three times a week, a total of seventeen treatments being given. After the fourth treatment he began to utter a few more words. After the fifth treatment articulation showed

marked improvement, and pronunciation was more distinct. He began to use the arm and hand, and for the first time he was able to make a fist. After the sixth treatment the patient himself stated that he felt much better. His eyes appeared brighter, and he could understand more easily. After the seventh treatment he noticed that the hand and foot were warm and that the feeling of numbness had disappeared. This patient was also subject to epileptic fits and had on an average from three to five each week. Since the beginning of diathermy treatment he has not had any attacks from March 9 until March 26, when he had another. He was treated regularly until April 16 and showed continued improvement in his general condition.

CASE 2.—J. Z., aged 63, had had left hemiplegia for eighteen months. He complained of paresthesia in the left arm and hand. Diathermy was applied to the brain with no untoward effect. After the second treatment the patient stated that for the first time in eighteen months feeling had returned to the fingers and that he experienced a peculiar sensation in both the upper and the lower extremity. The grip had improved considerably. Following the fourth treatment there was marked vertigo, which lasted for about ten minutes. The patient returned for another treatment and stated that he felt much better, but he experienced some pain in the third finger of the left hand. Treatments were discontinued temporarily.

CASE 3.—W. S., aged 45, had had left hemiplegia for one year. Application of diathermy to the head was begun on March 9, 1934, a dose of 650 milliamperes being given in thirteen minutes; the treatments were given three times a week. After the fourth treatment there was marked improvement in the circulation on the entire left side of the body, together with a peculiar tingling sensation. The patient stated that he felt better than he had done at any time and for the first time in a year had no nocturia. After the fifth treatment he was able to raise his arm above his head. The tremors in the arm and hand had stopped. The eyes appeared much brighter. After the sixth treatment the patient walked without assistance and without a cane, and the left side was much steadier. After the fourteenth treatment a son stated that the patient's condition showed such marked improvement, especially in mental faculties, that he was like himself again.

CASE 4.—G. M., aged 49, had had left hemiplegia for one year. He was given diathermy for twenty minutes, with a dose of 300 milliamperes. Following the third treatment he stated that he had more feeling in the left arm, slept much better and noted a tingling sensation in the arm. After the fourth treatment the mental attitude had improved. The left hand was warmer, and he was able to lift the hand well above the head; the tremors had disappeared. The gait showed marked improvement. After the fifth treatment he appeared wide awake, and his eyes were much brighter. Following the ninth treatment a peculiar incident occurred. The patient lost speech and the entire use of the left arm and leg for five minutes. Following this attack the arm and leg appeared much more relaxed, and speech was clearer. The patient always had to be assisted to the clinic. Following the tenth treatment he reported to the clinic unassisted, boarded a trolley car and appeared happy.

Comment.—An attempt was made to record the spinal fluid pressure in some of the cases. In one the initial pressure of the spinal fluid was 4; ten minutes after the treatment was begun the pressure was 32; twenty-five minutes after the beginning of treatment it rose to 40. The treatment was stopped, and the pressure immediately fell to 34, at which time 5 cc. of fluid was removed and examined for total protein, which was 23 mg. per cubic centimeter, and for cells, which numbered 2. In another case the initial pressure was 6. The total protein content after treatment was 16 mg. and the cells numbered 3. In another observation the initial pressure before treatment was 14; twenty minutes after the beginning of treatment the pressure had reached 23; after thirty minutes it fell to 19. The total protein content after treatment was 17.5 mg., and the cells numbered 3.

The blood pressure was taken during the treatment and showed no variation.

DISCUSSION

DR. TEMPLE FAY: Did the patients complain of headache at any time after the treatment was instituted? This method seems to me to constitute an interesting subject for analysis from two standpoints: hyperemia of the brain, if induced by diathermy, might account for the remarkable improvement noted in the cases which have been reported here. The fact that the pressure of the spinal fluid rose coincidentally with the improvement of symptoms indicates an increase in the volume of blood. When the pressure of the spinal fluid is low and cerebral function deficient there is usually a generalized or relative increase in cerebrospinal fluid or tissue fluid within the craniovertebral cavity. This increased volume of fluid is at the expense of the volume of circulating blood. In order to return sufficient oxygen and nutrition to the brain so as to improve various deficiencies of function, it is necessary to increase the volume of blood, but this can be done only when an equivalent amount of space has been yielded by the extensive accumulation of fluid. In the phase of hyperemia one would expect a rise in intracranial pressure, and with better circulation and available oxygen, increased absorption of fluid.

The fact that the clinical picture showed definite improvement in Dr. Martucci's cases, I believe, is supported by the observations regarding the increase in spinal fluid pressure.

I have noted the temperature of the surface of the brain to be 100.5 F., whereas if a thermocouple is introduced deep into the substance of the brain the temperature may be as high as 103 F. It would be interesting to note what changes in temperature the patient manifested during the period of diathermy treatment.

There may be contraindications in certain cases, as the diathermy is applied to an organ which normally has a temperature higher than that of other tissues of the body.

DR. BERNARD ALPERS: Was the objective improvement maintained in these patients or was it temporary even after a number of treatments? It is difficult to conceive that in a destructive lesion of this sort diathermy with hyperemia would produce changes in the brain that could make changes in the hemiplegia.

I wish to sound a note of warning with regard to the use of this current. One does not know just how high the temperature of the brain is raised with this treatment. It may have beneficial results at first, but high temperatures produce changes in the tissues of the brain. The fact that they do not show changes now does not mean that there may not be changes later if the temperature is raised high enough.

DR. W. L. LONG: Was there any change in the neurologic signs on repeated examinations? I wish to suggest that some measurement be made of the amount of oxygen contained in the blood, which is very susceptible to elevation or decrease; thus the rate of flow of blood through the brain may be determined.

DR. A. A. MARTUCCI: The temperature of these patients varied from normal to 99 F., but it never went above that point. The electrode behind the occipital protuberance was strapped to the shaved portion of the head. We used an electrode 3 by 4 inches (7.5 by 10 cc.) behind the occiput and one small electrode 2 by 3 inches (5 by 7.5 cc.) on the right or left frontal area, depending on the side of the hemiplegia. The electrodes were kept in place by bands of adhesive tape.

In answering the question concerning the number of milliamperes used, it depended on the resistance and tolerance of the patient. We used from 300 to 750 milliamperes of current. One patient could not tolerate over 300 milliamperes. Dr. Alpers asked about the improvement—how long it continued. The main subjective and objective symptoms have improved since treatment has been discontinued. All the patients have received treatment up to a recent period, however.

VENOUS ANGIOMA OF THE FOREHEAD WITH INTRACRANIAL COMPLICATION: REPORT OF A CASE. DR. CLARENCE A. PATTEN.

A Negro boy, aged 6 years, was first seen in my clinic at the Delaware Hospital, Wilmington, Del., on April 26, 1933. The chief complaint, as given by the mother,

was that the child did not use the left arm unless made to do so and that he dragged the left foot. The past medical history indicated that the child was born normally at full term and without difficulty. At birth, however, it was noted that he had, in the mother's words, "a bunch of blood vessels between his eyes." He progressed normally from the physical standpoint and at the age of 1 year was operated on at the Hospital of the University of Pennsylvania for removal of the hemangioma of the forehead. At the age of 2 he was operated on for hernia. Except for mumps and measles the child has had no infectious or contagious disease.

The mother stated that the tumor of the forehead seemed to be much smaller for a while following the operation but that from the age of 3 it had slowly and gradually increased in size and extent.

On neurologic examination the child showed no evidence of paralysis of the cranial nerves except a slight but definite weakness of the movements of the lower part of the face on the left. The left upper and lower extremities were distinctly weaker than the right, and the tendon reflexes were everywhere increased, the left, however, being much more active than the right. There was a definite bilateral Babinski sign which was more marked on the left. There was slight spasticity in the left leg as well as dragging of the foot when he walked. There was definite incontinence of urine but apparently no difficulty with the rectal sphincter. So far as could be determined there were no alterations of sensation. Mentally the child was distinctly defective.

From the general physical standpoint he was in excellent condition.

Laboratory and special investigations showed: (1) normal eyegrounds; (2) normal roentgenographic picture of the head and sinuses, except that the frontal sinuses were not developed; (3) negative Wassermann reaction of the blood, and (4) normal blood count and urine.

Examination of the mass in the midline of the forehead showed a soft, nonpulsating vascular tumor extending from the hair line down to the nose and spreading out into the region of the eyebrow on either side. Just above the nose in the midline a distinct depression in the bone was palpated, which was about the diameter of an ordinary lead pencil. It seemed to me distinctly possible that this depression was an opening through the skull through which blood vessels were coursing, but it was not demonstrable in the roentgenograms. The tumor varied in consistency, sometimes being rather soft and at other times tense, but always definitely compressible.

During the year that the child was under observation he began having convulsive attacks. These were described as generalized epileptiform seizures with unconsciousness shading off into semistupor and lasting for one or two hours. The neurologic findings have not changed except that through growth and education in the use of the left arm the child handles himself better. At present the left arm and leg are paretic, but they are spastic only on voluntary motion. The reflexes are generally increased, with the left greater than the right. The strongly positive Babinski sign has remained on the left, and there is a moderately positive Babinski sign on the right. The child walks fairly well but in attempting rapid walking shows spasticity of gait.

The condition was diagnosed as venous angioma of the forehead, possibly connecting with the superior longitudinal sinus. There is probably a hemangioma extending over the frontal lobes bilaterally, but more marked on the right side. There was no pulsation in the tumor on the forehead, and no bruit could be heard over the skull. There were no changes in the size of the carotid arteries and no disturbance of blood pressure or cardiac function. Because of these findings it was decided that the tumor was entirely venous and had no arterial connections. I believe that it is of congenital origin and that with the growth of the child there had been a continuing growth and extension of the tumor.

Several points of interest are brought out by this case. Associated extracranial and intracranial angiomas are not frequently encountered, less than 25 cases having been reported. Second, midline vascular tumors are less common than nevi of the

face or scalp in irregular locations. Third, cerebral vascular tumors are not frequent (2 per cent of all tumors of the brain according to Cushing and Bailey) and are rarely diagnosed except when associated with extracranial angiomas or when discovered by the characteristic parallel lines of calcification on roentgen examination. For the most part discovery is made at operation or necropsy.

Virchow described and classified cerebral vascular tumors in 1863, and Cushing and Bailey in their monograph in 1928 brought the subject up to date. Since then a few papers have dealt with the subject, a small number of additional cases being reported. All authors seem to be in agreement that malformations of the blood vessels are congenital and are classifiable into venous, arterial and arteriovenous angiomas. Cushing and Bailey expressed the belief that the true tumors are the hemangioblastomas; they occur principally in the regions of the fourth ventricle and are cystic. All types are difficult to treat. From a surgical standpoint little can be done because of the wide and irregular extension as well as the frequent inaccessibility when they penetrate into, or lie wholly within, the cerebral tissue. The best results are obtained by roentgen and radium therapy because of the embryonal character of the malformations and tumors.

Clinically, those of arterial or arteriovenous origin often produce choking of the disks and convulsive seizures. Venous angiomas rarely produce papilledema but may cause convulsions. Sometimes arterial connections are established later in the purely venous types, giving rise to the characteristics of arteriovenous tumors. Occasionally an arterial angioma causes an increase in the size of the vessels of the scalp, hypertrophy of one or both carotid arteries, lowered diastolic blood pressure, an increase in pulse rate and a bruit that can be heard over the site of the lesion and often over the carotid arteries down into the chest.

Dr. William G. Spiller: The patient in the case to which Dr. Patten has referred is related to a patient under my care who was admitted to the Hospital of the University of Pennsylvania on June 17, 1918. The statement was obtained from the mother that when she was three and one-half months pregnant she held on her lap a child who was being treated with roentgen rays. It may be that the fetus was affected by these rays. The birth was normal, but when her son was 2 or 3 months of age the right upper limb was observed to be paralyzed. When he was 1 year old the mother noticed that the right lower limb also was paralyzed; this hemiplegia probably had existed since birth. The child had telangiectases on the left side of the forehead, on the left side of the scalp near the hair line, on the left eyeball and on the back. Like Dr. Patten's patient, this boy had convulsions, but he did not have them until 1918, when he was 12 years of age and was approaching the period of puberty. I decided that he probably had telangiectasis of the brain. I requested Dr. Frazier to operate, and this lesion was found on June 26, 1918, in the left rolandic region. Only a few vessels were tied. The boy was much improved by the operation; the convulsions became infrequent, and at the time of the last report, April 11, 1919, he had not had any convulsions for six months.

This boy had associated movements. He could not close his right hand alone, but when he closed his left hand he could not keep his right hand open.

Dr. Temple Fay: Was the angioma sufficiently disfiguring to warrant surgical attention? An encephalogram might determine the question of cerebral extension.

Last year a patient presented the symptoms of a similar lesion situated in and about the right orbit. The hemangioma had destroyed the sight of the right eye when the patient was 6 years of age. When he was 24 years of age the mass protruded beyond the contours of the face. Dr. Babcock has been able to obliterate the hemangioma by repeated injections of quinine urea and sodium morrhuate; rapid thrombosis and obliteration of the lumens of the vessels were accomplished.

The method is simple, and the results are astounding. During the past eleven months the tumor has entirely disappeared, and the eye is now ready for a plastic operation and the introduction of an artificial eye.

If the encephalogram did not show too marked cerebral involvement, this method might be of value in Dr. Patten's case.

DR. CLARENCE A. PATTEN: In answer to Dr. Fay's question as to the disfiguration of the face, I do not believe that it means anything so far as this mother and child are concerned. The mother is principally concerned because the child has weakness of the left side and convulsive seizures. He is definitely mentally defective. As previously stated, the roentgenograms were poor, and I cannot tell about the vascular markings or whether there was calcification. I am particularly interested in the problem of treatment and appreciate the suggestion of injections into the vessels. Any procedure which will prevent convulsions and the extension of the hemiplegia will be worth while. The patient of whom Dr. Fay spoke had reached maturity before treatment was instituted. It is my impression that these vessels take on unusual growth with the growth of the patient, and that is my feeling with regard to this child. Perhaps some growths do not develop this way. I think that early treatment is important.

MANAGEMENT OF SPINA BIFIDA BY REPEATED DRAINAGE OF THE SAC. DR. GEORGE M. DORRANCE.

This is a preliminary report on drainage of the sac by puncture through the normal skin at least 1 inch (2.5 cm.) away from the sac.

In a review of the literature in an article by Gross and Sachs in the May issue of *Archives of Surgery* (**28**:874, 1934), they stated that surgeons may be divided into two groups in regard to their views on operation: those who favor operation at an early age, and those who take the attitude expressed in Frazier's book that operation should be delayed until the patient is a year or more old, except when rupture of the sac is imminent.

To my mind, there are two classes of cases: one in which the final result is worth while and the other in which the child dies whether treatment is instituted or not. The more I see of the different varieties of congenital malformation the more I am convinced that early operations are not desirable.

It is universally agreed that operation should not be performed until the granulation tissue of the sac is epithelized, otherwise it becomes infected. In other words, there is a group of patients who die before anything can be done, and there is another group in whom hydrocephalus will develop whether an operation is done or not. As many patients die before they are fit for surgical intervention, I introduced the method of frequent tapping to take care of them until they have a fair chance of undergoing a successful operation. The idea was first to relieve the pressure, for I knew full well that if extreme pressure within the sac is relieved there is more absorption of the cerebrospinal fluid than if the sac is in extreme tension, and second to prevent hydrocephalus in patients having a tendency in this direction.

Again I quote from Gross and Sachs: "While it is true that operations performed on infants more than a year old result in a much lower mortality, it must be remembered that many of the deaths might have been prevented by early operation. The mortality of children with spina bifida who are not operated on is appalling. In the report of the Clinical Society of London in 1885, 615 of 647 deaths from spina bifida occurred in infants less than 1 year of age. Consequently, the mortality of 35 per cent reported by Moore in a series of 385 cases (gathered from the literature) in children who were operated on when less than 1 year of age is not excessive. Harmer, in 1917, reported a mortality of 40 per cent in a series of 34 cases in which he performed operation. In this series there were 7 patients with meningocele; 23 with myelomeningocele and 4 with cranium bifidum. Twenty-two of the patients had ulcerated or leaking sacs, and of these only 9 survived. Cutler, at the Children's Hospital in Boston, analyzed 39 cases in which operation was performed. They youngest patient was 18 hours old and the oldest, 3 years. In this group there were 15 patients with single meningocele and 24 with myelomeningocele. Thirteen of the patients had ruptured or granulating sacs. The

mortality was 41 per cent. Of the patients who were discharged from the hospital, the end-result in 6 was unknown; 7 were living and well, 1 was living and improved, 4 were living but had complications and 4 had died. Of 18 patients on whom operation was not performed, 10 had died; the result in 6 was unknown, and 2 were alive."

In 1 of my 3 cases drainage was done frequently for months; in the other drainage has been done for the past six weeks, and I expect to continue this treatment as long as it is necessary.

In the first case (from the American Oncologic Hospital) the sac was covered with the usual thin material with a granulating surface. Much to my surprise, the more I tapped the sac the quicker the granulating material was covered with epithelium, and it is now completely covered. The sac increased greatly in thickness, which again was a surprise to me, and as far as I can determine there is no indication for operation. This case was more or less of a saccular type. The result is just as satisfactory as if I had operated. The removal of the sac would surely not be of any advantage to the child, and the operative mortality rate in such cases is very high.

In the second case (St. Agnes Hospital) at least four vertebrae were involved. The sac was of the wide, flat variety. When the patient was first seen the entire sac was covered with granulation tissue; as this was thin, rupture was expected to take place, and early hydrocephalus was apparently beginning. It was a question whether the child would live or not. With daily tapping there has been no infection; the fluid is clear; the sac is greatly thickened, and the granulation tissue is now almost entirely epithelized. The head is gradually enlarging. The child had paralysis of both lower extremities and therefore does not present a good operative risk.

In the third case (Oncologic Hospital) at least eight vertebrae were involved. The condition was hopeless. It improved considerably, so much that the child was allowed to leave the hospital. Weekly tapping was tried but was not satisfactory. The mother became dissatisfied and would not send the child to the hospital. The child died. The point to be noted in this case was that intermittent tapping was apparently of no avail. In order to be successful, one must carry out the procedure almost daily for weeks.

I know of no other method at present which is so easy and which is fraught with so little danger as this, nor any in which the sac epithelizes so rapidly and thickens. Surely the children who are not good operative risks should be given the advantage of this method. It seems clear to me from these 3 cases that this is a method of value.

The points to be emphasized are: The sac does not perforate, it becomes greatly thickened, the granulation tissue of the sac is epithelized much faster, and it seems to me that there is some effect on the hydrocephalus. This procedure should reduce the mortality in cases that are not suitable for operation.

DISCUSSION

DR. TEMPLE FAY: This important problem has been viewed in a new light by neurosurgeons during the past few years, following the work of Peet, in which transplantation of the pelvis of the kidney into the spinal canal permitted the constant drainage of cerebrospinal fluid in hydrocephalus. It has been noted that repeated drainage of spinal fluid in cases of meningocele has likewise brought about improvement.

Penfield read before the Section on Nervous and Mental Diseases of the American Medical Association in 1931 a paper concerned with the absorptive mechanism in certain types of meningocele. He pointed out that operation should preserve clusters of pacchionian tissue which occur about the margin of the spina bifida and the meningocele.

In discussing his paper (*J. A. M. A.* **98**:454 [Feb. 6] 1932), I emphasized that "dehydration" plus control of the formation of spinal fluid had yielded excellent postoperative results. I have noted shrinkage of the sac and the formation of

thick skin tissue over the defect when constant drainage of the spinal fluid was permitted as a result of the introduction of a silver cannula through the subarachnoid space and under the muscles of the back into the peritoneal cavity. Although the results in the 2 cases cited were ultimately unsuccessful because of erosion of the silver cannula through the tissues of the back, with secondary peritonitis, 1 infant survived four months with complete recession of the meningocele. I have used the method of Peterman in placing silk setons subcutaneously, radiating from the meningocele sac. This method of improved drainage of spinal fluid and "dehydration" and the limitation of fluid intake to 12 ounces (355 cc.) in the infant have permitted release of tension in the meningocele with better adjustment of the herniating parts of the cord.

As the herniation occurs, in my opinion, as a result of hydraulic pressure extending through a weakened spot or area of final closure during fetal life, it is desirable to control this factor by removal of spinal fluid and "dehydration" in the hope that the tissues may readjust themselves to a more normal position and the covering of the meningocele reach a state of permanent protection.

I agree with Dr. Dorrance that operation and repair of the meningocele cannot offer as good an end-result as the natural method of shrinkage and readjustment of tissues as demonstrated. I believe Dr. Dorrance's warning regarding early intervention should be carefully observed.

Dr. George M. Dorrance: What I was previously trying to accomplish was to keep the patient alive and get him in such a condition that an operation, if the surgeon decided to perform one, offered some chance of success. The immediate operative mortality in these cases has been around 40 per cent. After observing the results in these few cases I am inclined to agree with Dr. Fay that operation is to be avoided except as a last resort.

NEW YORK NEUROLOGICAL SOCIETY

Regular Meeting, Oct. 2, 1934

Israel S. Wechsler, M.D., *President, in the Chair*

Peripheral Facial Paralysis Caused by a Stab Wound. Dr. Bela Mittelmann.

A white man, aged 38, was stabbed behind the right ear four years ago; immediate paralysis of the right side of the face followed. The wound was packed and sutured, but the facial nerve was not seen by the surgeon. A mild infection developed, but the wound healed within two weeks. Sixteen days after the injury the patient still showed all the signs of peripheral facial paralysis. The sense of taste (chorda tympani) was intact. Examination showed complete lack of response to stimulation with faradic current and only slight and vermicular response to direct stimulation with the galvanic current.

Four months after the injury improvement of the muscle tone was noted. About the fifth month involuntary twitching appeared in the paralyzed muscles. Examination in the seventh month showed complete absence of response to direct or indirect stimulation with either the faradic or the galvanic current. There was a questionable return of function in the orbicularis palpebrarum. Opinions as to the necessity of surgical intervention were divided. About the tenth month there was from 15 to 25 per cent return of function. There was, however, still no response to any form of electrical stimulation in front of the ear.

About a year after the injury the following phenomenon was observed for the first time. Stimulation with either the galvanic or the faradic current over the scar behind the ear produced contractions in all the paralyzed muscles. The minimal current required to produce contraction was less than that required on

the normal side (normal side, 2.5 milliamperes; injured side, 1.5 milliamperes). The response to direct or indirect stimulation with the galvanic or the faradic current peripheral to the scar returned eighteen months after the injury. The contraction was vermicular, and a stronger current was required than on the healthy side (partial reaction of degeneration). At present the patient shows 80 per cent recovery of function; the facial nerve on the right side is still overexcitable at the site of the injury, and a partial reaction of degeneration is still present.

The interest in the case lies partly in the clinical course and partly in the presence of certain electrical phenomena. Clinically, the patient recovered without surgical intervention. Electrically, he showed total inexcitability to stimulation of any kind peripheral to the injury for eighteen months, but at the same time overexcitability of the facial nerve at the site of the injury. I have found no description of this phenomenon in the literature.

DISCUSSION

DR. BENJAMIN ROSENBLUTH: I wish to call attention to the fact that not only electrical but even normal voluntary response is increased on the affected side in so-called "recovered cases" of long-standing facial palsy. The affected side is weaker, and on testing the normal side voluntary action is increased; this corresponds to the electrical reaction. In some of my experiments on sectioned nerves I find that those in which there is the greatest amount of reaction in the proximal stump contain the greatest number of proximal axis-cylinders. In such cases there is the greatest degree of hyperirritability, especially to the faradic current.

A FOLLOW-UP STUDY OF HOCH'S CASES OF BENIGN STUPOR. DR. HYMAN L. RACHLIN (by invitation).

Dr. A. Hoch's monograph "Benign Stupor" appeared posthumously in 1921. Since, the benign stupor reaction has been recognized as a definite entity. It is classified as a phase of manic-depressive psychosis with a favorable prognosis. The stupor may occur alone or may replace a manic or a depressive attack. It is characterized by apathy, inactivity, negativism, disturbances in thinking and thoughts of death.

One of the 19 patients whose cases Dr. Hoch described died while under his observation. I have been able to trace only 13 of the remaining 18 patients. Of these, 9 are living, 6 in various state hospitals (1 is on parole at the present time), and 4 are dead. The conclusions are based on the review of Dr. Hoch's material and the additional facts from my follow-up study.

The follow-up study reveals that 13 of the 18 patients were available for study. Seven had clearcut cases of schizophrenia. Two are considered tentatively as having schizophrenia. The condition in 1 case was classified in the manic-depressive group, mixed type, and in another in the group of "psychosis with other somatic disease." As the condition in the 2 remaining cases shed no light on the problem, I prefer to leave them unclassified. All but 2 of the 13 patients were readmitted to hospitals for mental diseases. Three were admitted three times and 1, five times; these 4 patients are still in hospitals and show regression. What the outcome in the 2 remaining cases would have been had the patients lived is a matter of conjecture.

The follow-up study shows that regression has occurred in many of the cases. But since in Dr. Hoch's concept they represent a phase of manic-depressive psychosis, it follows that such a classification cannot be applied in these unfavorable cases. I, therefore, find little of diagnostic value in the benign stupor reaction; the diagnosis depends not on the differences between benign stupor and catatonia but on the underlying symptoms which differentiate manic-depressive psychosis from schizophrenia.

Stupor is known to occur in many conditions, organic as well as functional. The duration of the stupor is variable, and it may be deep or shallow. Deep

stupor of long duration is known to occur in cases of depression, whereas superficial stupor of short duration has been described in cases of schizophrenia. Patients suffering from organic psychoses of which the ultimate prognosis is poor have recovered from stupor which occurred in the course of the disease. It is therefore self-evident that the disease and not the symptom (in this case stupor) should be designated as malignant or benign.

Since schizophrenic reactions may occur in attacks, periodicity and recoverability are not distinguishing symptoms.

In summary, I find that all of the evidence points to the conclusion that stupor is a symptom of a disease and not a disease entity.

DISCUSSION

DR. ISRAEL STRAUSS: This excellent paper deserves favorable comment. Dr. Rachlin has shown how important the follow-up study is in psychiatric cases in which there are so many changes in the conduct of the patient over a long time, and how important it is to gage the relative importance of the various symptoms shown by these patients at different times during their life history. Of course, if Dr. Hoch were here I am certain that on hearing the history of these patients covering this long period he would agree that the mental disorder was malignant. I feel likewise that were he here and if he had listened to this presentation or had himself had the opportunity to make this study he would likely have discarded the concept.

DR. CLARENCE O. CHENEY: I have had the opportunity of reading Dr. Rachlin's paper in advance, not only the one presented here but another prepared in more extensive form covering a larger number of cases. In connection with Dr. Rachlin's remark that he was unable to trace more than 18 patients, it might be recalled that some of the 40 cases that were mentioned by Hoch in his study may have been cases of patients he had seen in the McLean Hospital before he came to New York, so that the material would not be available in this study. I am sorry that Dr. Kirby is not here to discuss this paper, because many of the original observations were made by him, as Dr. Hoch pointed out in his book. I think that it is also fair to call attention to the fact that the book was compiled by Dr. McCurdy after Dr. Hoch died. Only five chapters of the book had been written by Dr. Hoch before he died. Dr. McCurdy had the feeling that he expressed Dr. Hoch's opinions in the other parts of the book.

I recall the second case that Dr. Rachlin mentioned—that of a woman whom I had seen in 1917. She was the one who had had a previous attack and had been regarded as having recovered, having had a residence outside the hospital for ten or eleven years. In 1917 she was readmitted. This was, and still is, a most interesting case. The patient remained for the most part in bed in an inactive, immobile state; her face had a wooden expression, except for movement of the eyes, which indicated that she seemed to have some interest in things. The most striking characteristic of her condition was that she would suddenly, without warning, come out of the inactive state and play pranks. She would jump over the beds and dance around in a free and graceful manner, as she had done in her previous social activities; she seemed to be having a good time during these few minutes, all without a word or any play of facial expression. On the other hand, at other times she would break out of her mute state, become profane, tell the doctors exactly what she thought of them and then suddenly sink back into the inactive state. At that time it was doubted whether the prognosis was good because of her make-up. She had a poor foundation, a difficult family situation and an unhappy married life. It was felt that she had little incentive to get well, and I am not surprised that she has not improved. I am not at all satisfied that she has dementia praecox at the present time, and that applies to the other patients whose condition was classified as schizophrenia by Dr. Rachlin. I think that this patient was "spoofing" him when she gave the false, long name she spelled out. The history indicates that she may have had spells of inactivity and then outbursts of overactivity. But from what was known of her in 1917 she did not

show at that time the characteristic symptoms of a catatonic dementia praecox reaction, and personally I am not at all satisfied that she does now.

Dr. Rachlin's main conclusion is that Hoch's concept of the symptom complex of benign stupor has no value. I think that Dr. Hoch made a contribution. If one reads his book one gets a better idea than from reading a paper epitomizing its contents. The point is that the attacks of stupor which he described do end in recovery. The patients had had previous manic-depressive attacks, and a number of them had subsequent manic-depressive attacks from which they recovered. One of the patients subsequently was readmitted to the hospital five times. Dr. Hoch described benign stupor as a syndrome. He realized that these attacks of stupor occur in other conditions, and the arguments and conclusions of Dr. Rachlin regarding this seem to be beside the point. He described benign stupor as a clinical syndrome with certain cardinal symptoms, emphasizing the inactivity, catalepsy, negativism, preoccupation with death and tendency to recover. Dr. Rachlin said that Hoch classified "benign stupor as a phase of manic-depressive psychosis resulting in a favorable prognosis." The actual fact is that on page 206 Hoch said: "It is probably safe to assume that . . . the symptoms of stupor per se imply no bad prognosis." If one reviews his conception of the mechanism one sees that he considered these reactions of stupor as a deep regression. I am not certain that it was ever definitely stated, but it might be implied, on the basis of knowledge of Hoch, that he would feel definitely that regression at any one time to the depth of a stupor indicated at least a poor adjustment, and that the outlook for the person's future adjustment was not necessarily good. I have reason to believe that Dr. Hoch did not think that if a patient recovered once from an attack of stupor he was always going to stay well or that in subsequent attacks he might not stay ill. I believe that he thought the adjustment in that patient's life was poor because of the evidence shown by regression to stupor. But what he was describing was a type of stupor different from the chronic progressive catatonic deterioration. Hoch knew well that many of these patients made attempts to commit suicide. The point that other groups of patients tend to commit suicide is somewhat beside the question. Hoch's thesis is that stupor may be replaced by attempts at suicide. The stupor is a state of inactivity; the attempt at suicide represents breaking through that apathy or inactivity and an attempt to do something.

Benign stupor still exists, I believe, and if there are patients who have had an attack of benign stupor once and subsequently did not get well, this does not detract from the contribution which Dr. Hoch made.

Dr. Samuel W. Hamilton (by invitation): August Hoch was one of the keenest psychiatrists in this country during two decades at the turn of the century. He found it the current diagnostic practice—which indeed is the same now as then—to bundle together in one huge group a great many cases that develop in the first half of life and usually do not end in recovery. These usually went under the title "dementia praecox," though Bleuler's term "schizophrenia" was already accepted by many. To be sure, the groups of cases described under these titles by Kraepelin and by Bleuler were not exactly the same, but the differences were not important. Whatever the standards of diagnosis on the part of diagnosticians, there were some patients who recovered. The stricter-minded called these states of restoration "recovery" if they occurred in cases of some other disorder and "remission" if they occurred in cases of dementia praecox.

Out of this huge pile of psychiatric discards Dr. Hoch picked a group of cases that seemed to him different, not only in outcome but also in symptomatology. He studied them with characteristic thoroughness. It is appropriate to say that Dr. Hoch gave much weight to Dr. Kirby's studies as a basis for some of his own formulations. He found somewhat similar views in the writings of Pinel and Dagonet and particularly of Newington.

Another physician has reviewed the histories of some of these patients to see what the outcome has been. This is a valuable project and, whatever the conclusions, one must give credit to Dr. Rachlin for a careful study. Whether my

opinions agree with or differ from his is of slight consequence. Probably he wanted me to be the *advocatus rei absentis.*

To one who has followed the histories of many patients not only is it obvious that some get well in whose cases the diagnosis of dementia praecox seems justified, but it is just as evident that patients who have attacks of the manic-depressive variety either do not get well, their condition running a circular course or even a manic course for many years, or have "ups and downs" over several decades. It is also true that patients with sufficiently typical manic attacks sometimes show a chronic state in the latter part of their lives. One might then conclude that the earlier diagnosis was wrong and that the condition was really dementia praecox from which the patient recovered once or two or three times but which in some mysterious way was really progressing all the while toward dementia praecox. These differences in mutually exclusive diagnoses incline one to the position taken by such a man as Cotton, for instance, who liked to combine all the so-called functional psychoses and not try to split them into categories. Most psychiatrists have the opposite inclination and would like to possess criteria by which they could at least cut the huge group of cases of dementia praecox not into mere subdivisions but into some fairly definite independent groups.

Hoch said that the leading symptoms in his special group are poverty of affect, inactivity, catalepsy, negativism, wetting and soiling, thought disorder, preoccupation with death and a low grade fever. In these cases he found a strong tendency to recovery, an inclination to repetition of the sickness and a rather frequent appearance of manic states, retarded depressions or states of perplexity. He said, therefore, that this kind of stupor should be called benign and that it is a type of the manic-depressive psychosis. He pointed out in the typical cases some differences from the malignant stupors and described both typical and atypical forms.

Dr. Rachlin traced 13 patients and believes that the diagnosis of benign stupor is hardly justified. Since the prognosis is one of the issues in this discussion, the following brief case reports will show what has happened to the 13 patients.

Case 1.—After admission the patient was not well for thirteen months. She had a period of mild elation in the second year and another severe attack in the third year. Dr. Rachlin found that she made a good social recovery. She did not like to be reminded of her experiences in the hospital, and therefore Dr. Rachlin considers that she has emotional inadequacy and catatonia.

Case 2.—This patient recovered in eighteen months. Eleven years later she came back to the hospital in a state of acute excitement, and she died two days later. Dr. Rachlin considers this five day period of excitement undeniably typical of catatonia. One may well be less positive about the character of a wild excitement that terminates fatally with high grade fever.

Case 5.—This patient remained in the hospital seven months. After that she continued to have trouble with her husband. Dr. Hoch considered her quite well six years after discharge. She evidently drank to excess and she died eighteen years after discharge of chronic encephalitis, retroversion of the uterus and chronic alcoholism. Dr. Rachlin ventures no opinion as to her mental ailment; I certainly can see no reason for changing Dr. Hoch's analysis or conclusions.

Case 6.—This patient was a little older, having been first admitted to the hospital at the age of 28; the attack followed labor and operation. Another attack occurred twenty-five years later, with some relation to systemic syphilis. The diagnosis on the second occasion was psychosis with cerebral arteriosclerosis. Dr. Rachlin was impressed by the relationship to other somatic diseases. This is no sound reason for objecting to the formulation that was made at the time of the first attack; somatic diseases set off all sorts of reactions, and it is not especially infrequent to find in an organic psychosis of the fifth decade a history of an antecedent psychosis in earlier life. There are as yet no data on which to predict that a person at the age of 30 will have arteriosclerotic psychosis at 50. There may be reason to think that his psychosis at 50 is likely to end well, and that happened in this case, though the patient did not develop full insight and was somewhat uneasy about her future.

CASE 7.—This woman recovered in four months. Her condition was considered partial stupor. She went back to Ireland and died of tuberculosis a few years later. The reviewer dismisses the case rather casually.

CASE 8.—The patient recovered in nineteen months. Three years later she had a similar attack in another hospital, which lasted only six months. After four years she again became excited and recovered. After another three years she talked to herself and threatened violence, and for eighteen years she has been under care in the hospital. She was distractible and silly when she entered the hospital eighteen years ago. For the past eight years her conduct has fluctuated between excitement and subdued behavior. Interestingly, Dr. Rachlin found no history of delusions and no bizarre behavior. This is an unhappy outcome, but from a logical standpoint not so different from what is unfortunately seen in cases of straightforward manic-depressive psychosis without stupor at any time. Some patients with this condition spend long years in the latter part of their lives as social invalids in a hospital.

CASE 9.—This patient was under care in a hospital for two years. Afterward she had many attacks of depression; she was sexually promiscuous and industrially unsatisfactory. Eleven years after discharge she had another definite attack, and two years later, on being swindled out of $300, a state of excitement developed which was still in progress three years after readmission. The patient is of poor intellectual capacity. Dr. Rachlin thought that he uncovered auditory hallucinations, but one may be pardoned for thinking his examination inconclusive. If Dr. Rachlin, like Kraepelin, would restrict his diagnosis of manic-depressive psychosis to a strictly limited group of cases and classify other psychosis as dementia praecox his conclusion about this case would be correct.

CASE 10.—This patient's first residence in the hospital lasted over two years, and she has been sick most of the time for twenty years. Dr. Hoch remarked that in the first stage there was much sudden laughter, reminding one of that of dementia praecox, except that it was never shallow or silly. Dr. Rachlin avers that the patient never showed stupor. Dr. Hoch spoke of the patient as inactive and mute, sometimes offering resistance by making herself stiff and tense; she was given to wetting and soiling herself; she had to be fed by tube and did not laugh. After she began to dress herself and eat she remained for the most part very inactive for months; most psychiatrists would call this condition stupor. A year after discharge she had another attack, and it was said that a period of depression had lasted ten days during that interval. The second residence in the hospital lasted a year, and then the patient did well for six years. Her last residence in the hospital has lasted eight years. She dresses oddly, carries magazines and notebooks about, runs from a physician, chatters, laughs shrilly and talks incoherently. Even so, she discloses no frank hallucinations or delusions. Dr. Rachlin criticizes the previous diagnosis; no doubt it would be equally easy to raise objection to the diagnosis of dementia praecox if that should be made now, though the patient does disclose a deterioration of interest.

CASE 12.—This patient entered the hospital in her second attack, which lasted a year. Another attack occurred six years later and lasted six months. The fourth attack came three years after that. Twelve years later she had another attack of excitement; she seems to have recovered from that also. Dr. Rachlin does not agree with the diagnosis and remarks that any disturbance or incongruity among the primary mental symptoms indicates a schizophrenic reaction. He finds incongruities in the stupor phase and also in subsequent attacks. He thinks that the patient had not completely recovered in the intervals, but perhaps he has not presented this view conclusively. In her last convalescence the patient thought that she should not ever have been hospitalized and could not account for some of her ideas. It hardly seems justifiable to classify this case as one of dementia praecox.

CASE 17.—This patient recovered in four months. Another psychosis occurred five years later. She went to work and had two unsuccessful marriages; when

work failed during the depression she had difficulty with her relatives, and she now shows little drive. A psychiatrist has seen her recently and thinks she has a manic-depressive psychosis. Dr. Rachlin asserts that her efficiency has diminished. I hesitate to subscribe to this until I see what she does when times are better.

CASE 18.—Dr. Hoch remarked that this patient showed inactivity, apathy and a coincident subjective perplexity. She recovered in seven months and for two and a half years appeared well. During this time she bore two sons. She disliked her husband's family and grew increasingly bitter. Then she believed that the neighbors and the apartment house superintendents were molesting her. In 1920 she became highly religious but would not accept her clergyman's counsel. In 1926 she spent three days in the Bellevue Hospital after attacking her husband. She thinks that peddlers and a former hospital physician are in league with her husband to incarcerate her; she permits no strangers in the home and will not allow a telephone to be installed. This is evidently a pronounced paranoid condition; if you will, schizophrenia.

CASE 19.—This patient had an attack lasting six months. Nine years later she had a peritonsillar abscess followed by bronchitis with fever. Her psychosis was considered as "related to the other somatic diseases," and lobular pneumonia caused death in two months. Dr. Rachlin classifies this case as one of schizophrenia on the ground of the regressive behavior in the attack described by Dr. Hoch.

Thus, 2 of the 13 cases may need reclassification. This is not enough to render the concept of benign stupor useless.

A few words may be addressed to Dr. Rachlin's argument. He is much influenced by Bleuler's views, and rightly so, but one need feel no necessity on that account for disregarding what Hoch has said. Erroneously, I think, he intimates that Hoch considered benign stupor a special disease. Rachlin says that the differentiation of stupor depends on the analysis of the causative factors. Hoch said that in addition a prolonged observation may be necessary. Hoch was the more conservative. Nor can I see anything to criticize, except the diction, in Hoch's statement that when the four symptoms—apathy, inactivity, thinking disorder and absorbing interest in death—occur alone, one is justified in making a diagnosis of stupor. He apparently meant when the four converge without the presence of other important symptoms. I cannot see that he suggested, as Dr. Rachlin thinks, that every patient presenting inactivity or every patient presenting an absorbing interest in death shows stupor. Why should he object to Dr. Hoch's statement that suicide and stupor are related? He saw them together, and his experience has probably been paralleled by many.

I repeat that Dr. Rachlin has done a useful service. One need not agree with his conclusions, but one should value his work.

DR. PAUL SCHILDER: This discussion is of extreme general importance to psychiatry. Should one adhere to the rigid kraepelinian concept, or should one be more interested in syndromes than in rigid disease entities? No clinician will doubt that there is one type of stupor in which, despite regression, an important part of the personality is still intact. This part of the personality retains its relation to other persons and to the outside world. This is the type which Hoch called benign stupor. It is different from the rigid catatonic stupor which one sees in clearcut cases of schizophrenia. The course in cases of benign stupor is different from the typical course in cases of schizophrenia. The clinical picture, psychology and course are in some degree specific. Hoch's original study shows rightly the important part personality factors play in the genesis of the syndrome. These cases have also, according to Rachlin's follow-up study, a definite course different from that in cases of dementia praecox.

It would be interesting to know more about the family history and the body structure of these patients. I do not doubt that a better knowledge in this respect would give a deeper understanding of the nosology of the syndromes which are psychologically so clearcut.

DR. JOSEPH SMITH: I was fortunate enough to have been one of Hoch's pupils during my early days at a state hospital, and I remember that the question

of stupor and stuporous states came up for discussion. Soon after returning to the hospital I had an opportunity of observing closely a case of stupor in a young man. He made a complete recovery, and I was able to follow his case for two years. I have now under my care a woman aged 50, who has been subject to manic-depressive attacks for over twenty years; they recur almost every year. These attacks will last from three to four months and end in recovery. At present she is in a state of stupor. In depressed states partial stupor is common; complete stupor, rather rare. One should be able to define benign stupor and differentiate it from what is known as catatonic stupor. The catatonic case gives the impression of a voluntary regression, of a peculiar attitude on the part of the patient which is in agreement with his other bizarre activities. Hence sudden, impulsive and meaningless actions are common in cases of catatonia but are not observed in cases of benign stupor in which the activities are not strained but appear natural and are not subject to explosive variations.

DR. ISRAEL STRAUSS: I warned Dr. Rachlin that the work he was undertaking was a dangerous task. As I said at the beginning, if Dr. Hoch were here he might modify some of his concepts with the history of these cases in his possession. Dr. Rachlin has based his diagnoses in these cases on the knowledge he has gained from his study of the various psychiatric syndromes. When Dr. Rachlin makes his concluding remarks, I want him to speak of the 139 cases which he is following in respect to the incidence of benign stupor. I think that he will show that in state hospital services there has been a gradual disappearance of this concept. That does not mean that the cases described here do not occur today; it must mean some change in the conceptions used by psychiatrists.

DR. HYMAN L. RACHLIN: It is obvious that this problem is being attacked from conflicting points of view. If one follows Kraepelin he will reach one conclusion; if he agrees with Bleuler he will reach an entirely different opinion. All of this serves to confuse the issues and accomplishes nothing. Of necessity, therefore, one must make a choice and try to reach definite conclusions.

All agree with Bleuler that schizophrenia is not one entity. I think, therefore, that my results have not vitiated the work of Dr. Hoch. However, I believe that the majority of his cases are instances of schizophrenia, even though not of the type of schizophrenia described by Kraepelin. Many schizophrenic patients exhibit periodic attacks. The course of the psychosis is definitely that of a schizophrenic reaction. Every physician in a state hospital has seen such patients recover and remain apparently well for ten or fifteen years. During these years they make good social adjustments and then for some reason have other attacks.

It is plain that accurate conclusions will not be reached until the etiology of both schizophrenia and manic-depressive psychosis is known.

Dr. Schilder said that the cases which Dr. Hoch described and which I placed in the schizophrenic group run a different course from typical cases of schizophrenia, and since they run a different course he objects to my grouping them in this way. That may be true, but they also did not run a typical course of manic-depressive psychoses, so why put them into that group? One must therefore choose a new road which is somewhere midway between these two large groups.

I regret that I cannot answer Dr. Strauss fully. He has correctly anticipated part of my results. In tracing the 130 cases I plotted a curve for the number of cases of benign stupor which were diagnosed during the years following the appearance of Dr. Hoch's book. Allowing a couple of years for the recognition and the dissemination of this concept, one finds a gradual rise in the number of cases so diagnosed. But after the peak of the curve has been reached, one finds a gradual decline in this curve, so that by 1932, at the time when I began to investigate this problem, there were practically no diagnoses of benign stupor made in the Manhattan State Hospital, where there is an average admission of 2,400 patients annually, yet the percentage of manic-depressive cases has remained the same.

THE HISTORY OF NEUROLOGY. DR. ISRAEL S. WECHSLER (presidential address).

This paper will be published as a part of a book which is now in the hands of the publisher.

Book Reviews

New Introductory Lectures on Psycho-Analysis. By Sigmund Freud, M.D., LL.D. Translated by W. J. H. Sprott. Price, $3. Pp. 257. New York: W. W. Norton & Company, Inc., 1933.

"The whole time that I have been preparing the lectures I am giving you, I have been struggling with an internal difficulty. I feel, as one might say, uncertain of the terms of my licence. It is quite true that in the course of fifteen years' work, psycho-analysis has altered and grown; but in spite of that, an introduction to psycho-analysis might be left unchanged and unexpanded. It is always at the back of my mind that there is no *raison d'être* for these lectures. For analysis I say too little and nothing at all that is new, while to you I say too much and relate things which you are not in a position to understand and which are not for your ears. I have looked about for excuses, and have tried to justify each of my lectures on different grounds. The first, the one about the theory of dreams, was intended to put you back at once into the atmosphere of analysis, and to show you how durable our hypotheses have proved themselves to be. I was tempted to give the second, which traced the connection between dreams and the so-called occult, by the opportunity it afforded of saying something about a field of research in which at the present time prejudiced expectation is struggling against passionate opposition; and I allowed myself to hope that you would not refuse me your company on this expedition, but would follow me with a judgment educated to tolerance by example of psycho-analysis. The third lecture, which dealt with the anatomy of the personality, certainly made the severest demands upon you, so strange was its subject-matter; but it was quite impossible for me to withhold from you this first contribution to ego-psychology, and, if we had been in possession of the material fifteen years ago, I should have had to mention it then. Finally, the last lecture, which you had probably followed only with the greatest difficulty, contained some necessary emendations and new attempts at the solution of the most important problems; and my introduction would have been positively misleading if I had kept silent about them. You see how it is that when one tries to excuse oneself, it comes out in the end that everything was inevitable, that everything was pre-ordained. I submit to fate; and I beg that you will do the same."

With this résumé Freud begins chapter 5 of his new introductory lectures. Chapter 6 is on "Explanations, Applications and Orientations," while the last chapter is "A Philosophy of Life." Each of these chapters is numbered in sequence to his "Introductory Lectures on Psycho-Analysis" (1917), so that Chapter 1 is Lecture XXIX. These lectures were never delivered, because the author's age relieved him of the duty of lecturing in the University of Vienna and because a surgical operation rendered him incapable of addressing an audience. The new lectures were written as a continuation of the former volume, as a critical revision dealing "with matters which either did not exist in psycho-analysis at the time of the first lectures, or about which too little was known at that time to justify a special chapter-heading."

The chapter on the "Revision of the Theory of Dreams" does not bring out anything particularly new, but it gives an excellent brief description of dream formation. "The introduction: the wish to sleep, the voluntary with-drawal from the outside world. Two things follow from this: firstly, the possibility for older and more primitive modes of activity to manifest themselves, i. e. regression; and secondly, the decrease of the repression-resistance which weighs on the unconscious. As a result of this latter feature an opportunity for dream-formation presents itself, which is seized upon by the factors which are the occasion of the dream; that is to say, the internal stimuli which are in activity. The dream which thus eventuates is already a compromise-formation; it has a double function; it is on the one hand in conformity with the ego ('ego syntonic'), since it subserves

the wish to sleep by draining off the stimuli which would otherwise disturb it, while on the other hand it allows to a repressed impulse the satisfaction which is possible in these circumstances in the form of an hallucinatory wish-fulfilment. The whole process of dream-formation, which is permitted by the sleeping ego, is, however, under the control of the censorship, a control which is exercised by what is left of the forces of repression." To understand what takes place in a dream, one must study the phenomena of condensation, misplacement, distortion and symbolism. These make up the dreamwork which transforms the latent dream thoughts into the manifest dream. Understanding this "has given us our first glimpse into those processes which go on in our unconscious mental system, and shows us that they are quite different from what we know about our conscious thought, and that to this latter they must necessarily appear faulty and preposterous."

There can be no doubt that Freud's understanding of dream phenomena has given to psychology and psychiatry a lead in a most important direction—the understanding of primitive thinking, of "grammarless speech," of "the raw material of thought." One feels that these are valuable contributions, but the dogmatic interpretation of symbols, and the insistence on the thesis that "all dreams are wish fulfilments," are not so easily accepted. Freud brings up two serious difficulties to the wish fulfilment theory of dreams: first, that persons who have suffered traumatic shocks frequently dream of the old traumatic situation with horror, and, second, that so many dreams deal with painful anxiety related to the sexual experiences of childhood. He states: "In my opinion we ought not to shirk the admission that in such cases the function of the dream fails," but goes on to beg the question and assert that after all the dream may be an *"attempted"* wish fulfilment, and "at any rate the exception does not do away with the rule." This is bad enough heresy to the accepted tenets of scientific procedure, but when he indicates that his arguments are sound only "for those who have an understanding for the dynamics of the mind" he is creating an inner circle, a cult which knows the real truth. He would have done better to have admitted outright that the old theory was wrong. One cannot cast aside all the "rules of the game" and still "play the game" of science. The subject is complex and difficult; but that is no reason for allowing wishful thinking to replace logic; on the contrary, psychologists must be particularly careful of their observations and controls, for, as Freud himself asserts, "here (in psychology) the constitutional incapacity of men for scientific research comes into full view."

As for symbolism, it is the old story of being too dogmatic. Any one admits the importance of symbolization in thought and speech, and all agree that Freud has taught psychologists much about primitive thinking by his work on symbols. There are many, however, who cannot agree that such objects as a staircase, a cloak, a spider or a bridge always symbolize the same thing, no matter in what connection they come to mind. In his "Introductory Lectures on Psycho-Analysis" Freud was much more prone to be dogmatic, frequently using such terms as "always," invariably" and "in every case;" in the present volume these words crop up less often, but there is no excuse for using them at all when discussing the reactions of such a highly organized biologic unit as man. Variability is the rule. In this chapter it is pleasing to see that he states that "in almost every dream is incorporated a memory trace of . . . the previous day", but the word "inevitable" crops up once; "absolutely certain" is used, and "all" and "always" each appear. Certainly no scientist can accept such positive statements *ex cathedra*. One cannot ask that the evidence be presented in a lecture of this sort, but scientific usage insists on a more modest presentation of theoretical material.

Freud quotes the physicians of an American university "who only recently refused to allow that psycho-analysis was a science, on the ground that it admits of no experimental proof." Of course experimentation in its narrow sense is not the only tool of science; clinical observation and the analysis of accumulated data are older and equally honored methods. But there is a certain artistry in Freud's writing, a great ability to word things in an appealing way; then, before the reader becomes suspicious of the logic, he is disarmed by modest and apologetic phrases

like "If one has humbled oneself all one's life long in order to avoid painful conflict with facts, one tends to keep one's back bowed in one's old age before any new facts which may appear." This way of writing and the great human interest of the book, with its many passages showing keen insight and almost inspired intuition, take hold of the rapid reader and convert him to the author's point of view. Careful reading, however, has left the impression on the reviewer that the author is a great man, certainly, but not a scientist. Rather is he an artist and a philosopher, with an intuitive faculty which sees deep into human nature. He weaves theories and explains human activities. All great authors and some philosophers have done this, but it is not science.

Lecture XXXIV is a readable defense of some of the more disputed points in psychoanalysis, with a description of the uphill fight that Freud has had to obtain academic recognition. He insists, however, on complete loyalty to his teachings, which is obviously impossible. For example, he states: "The structure of psychoanalysis, although unfinished, nevertheless already possesses a unified organization from which one cannot select elements according to one's whim." It is dangerous to take a statement from its context and quote it; but the spirit of these pages (with the repudiation of Adler, Rank and the "partial believers") is: "We reject anything that contradicts our views." Fortunately, most of those who admire Freud's great contributions will go on examining the theories one by one and asking for evidence.

There is a good exposition of the relationship of psychoanalysis to education. In the beginning "our first intention was, as you know, to understand the disturbances of the human mind, because an astonishing experience had shown us that in this case understanding and cure go almost hand in hand and that a practicable path leads from the one to the other. And for a long time this was our only intention. Then, however, we came to recognize the close relationship, in fact, the underlying identity, subsisting between pathological and so-called normal processes. So psychoanalysis became 'depth-psychology'; and, since nothing that man makes or does can be understood without the aid of psychology, the applications of psychoanalysis to numerous fields of knowlegde, and especially to the mental sciences, came about automatically, forced themselves on our attention and demanded elaboration. Thus the application to education was brought up, for in working with a neurotic one always was led back into early childhood experiences, and one came to realize that the difficulty of childhood consists in the fact that the child has, in a short span of time, to make its own acquisitions of a cultural development which has extended over tens of thousands of years." He has to attain instinctual control and social adaptation. Much of this must be forced on him by education. The function of education is "to inhibit, forbid and suppress. . . . Education has therefore to steer its way between the Scylla of giving the instincts free play and the Charybdis of frustrating them. Unless the problem is altogether insoluble, an optimum of education must be discovered, which will do the most good and the least harm. It is a matter of finding out how much one may forbid, at which time and by what methods. . . . When, therefore, one comes to think of the difficult tasks with which the educator is confronted; when one reflects that he has to recognize the characteristic constitution of each child, to guess from small indications what is going on in its unformed mind, to give him the right amount of love and at the same time to preserve an effective degree of authority, then one cannot help saying to oneself that the only adequate preparation for the profession of educator is a good grounding in psychoanalysis. The best thing would be for him to be analyzed himself, for, after all, without personal experience one cannot get a grasp of analysis. The analysis of teachers and educators seems to be a more practicable prophylactic measure than the analysis of children themselves; and there are not such great obstacles against putting it into practice."

Other important subjects are equally well discussed in this chapter. Neuroses are said to be "serious, constitutionally determined affections, which are seldom restricted to a few outbreaks, but make themselves felt as a rule over long periods of life, or even throughout its entire extent. Our analytic experience that we can

influence them to a far-reaching degree, if we can get hold of the historical precipitating causes and the incidental accessory factors, has made us neglect the constitutional factor in our therapeutic practice. And we are in fact powerless to deal with it; but in our theory we ought always to bear it in mind." The discussion of psychoses and hormones is less enlightening.

Lecture XXX, "Dreams and the Occult," is an interesting interlude in an otherwise heavy book. It is well written, and the evidence for the theories expressed is given. Freud believes that there is "a heavy weight of probability in favor of the reality of thought transference."

The unfortunate chapter, "The Anatomy of the Mental Personality," Lecture XXXI, reveals a great man at his worst. The concept of the ego, the super-ego and the id is described in many words and with many varying similes and metaphors. The origin of the idea of such an "anatomy of the mental personality" is described thus: "From the symptom the path of psychoanalysis led to the unconscious, the life of the instincts, to sexuality, and it was then that psychoanalysis was met by illuminating criticisms to the effect that man is not merely a sexual being but has nobler and higher feelings." Thus Freud "formed the idea that the separating off of an observing function from the rest of the ego might be a normal feature of the ego's structure. . . . There is hardly anything that we separate off from our ego so regularly as our conscience and so easily set over against it. . . . Since the process of recognizing a thing as a separate entity involves giving it a name of its own, I will henceforward call this function in the ego the 'super-ego'."

All this seems simple enough, but reading on one finds that the simple "anatomy" is complicated by the dynamic functions; the workings of the ego, id and super-ego may be unconscious, preconscious or conscious. Then even greater complexities and vagaries are brought in when the three are compared and their positions elaborated. The essential character of the id is that "of being foreign to the ego. . . . Instinctual cathexes seeking discharge—that in our view, is all that the id contains." Yet "the ego is after all only a part of the id." Such statements are merely examples of the confused exposition. The three theoretical realms of the mental apparatus are described and redescribed. On one page adjectives are taken from chemical, electrical, military and political sciences. "The poor ego has a still harder time of it; it has to serve three harsh masters." Such anthropomorphic romance cannot help antagonizing sound scientists. The chapter is an artistic and seductive exposition of a speculative philosophy, driven home by repetition and analogy ad nauseam.

Lecture XXXII, "Anxiety and the Instinctual Life" brings in some important contributions concerning anxiety states in neurotic persons. Whenever the author discusses clinical data he is convincing, especially when discussing the early origin of fear, such as the fear of the loss of love. He believes that anxiety is the reproduction of an old danger-threatening event. The description falls short because of his apparent lack of knowledge of the physiology of fear as demonstrated by Cannon, although he hints at it by stating: "The findings of psychology takes us to the frontiers of biological facts.

"Every stage of development has its own particular conditions for anxiety; that is to say, a danger-situation appropriate to it. The danger of mental helplessness corresponds to the stage of early immaturity of the ego; the danger of loss of object or of love corresponds to the dependence of the early years of childhood; the danger of castration to the phallic phase; and finally, fear of the super-ego, which occupies a special position, to the period of latency. As development proceeds, the old conditions for anxiety should vanish, since the danger-situations, which correspond to them, have lost their force owing to the strengthening of the ego. But this only happens to a very incomplete degree. A great many people cannot overcome the fear of loss of love; they never become independent enough of the love of other people, and continue their infantile behaviour in this respect. The fear of the super-ego should normally never cease, since it is indispensable in social relations in the form of moral anxiety, and it is only in rarest instances that an individual succeeds in becoming independent of the community." Thus theory

and observation are brought together. Especially clear is the recapitulation of the different phases of "organ-pleasure," each with its "erotogenic zone" and all related to sexual instincts. The earlier "pregenital" phases are the "oral," the "sadistic and anal" and the "phallic." The "genital" comes after puberty. The importance of these childish modes of thought and "deep-lying connections" is emphasized, and the reader gains the impression that wide clinical experience justifies the emphasis and the classification. The emphasis on the "birth-trauma" as the first great fear experience strikes one as overdrawn, for "the ego is the only seat of anxiety," and one wonders how much ego a child has at the moment of birth.

Instincts are discussed at length; the first proposition is that the two main categories of instincts correspond to the two great needs—hunger and love—subserving self-preservation and race-preservation. These are also called the "ego-instincts" and the "sexual instincts." So far the discussion has been helpful in explaining psychologic observations. But as the argument proceeds it becomes more involved. A sort of definition of Freud's conceptions of what an instinct is is given in these two passages: "An instinct differs from a stimulus in that it arises from sources of stimulation within the body, operates as a constant force, and is such that the subject cannot escape from it by flight as he can from external stimulus. An instinct may be described as having a source, an object and an aim. The source is a state of excitation within the body, and its aim is to remove that excitation. . . . The instincts do not only dominate mental life, but vegetative life as well, and these organic instincts display a characteristic which merits our most serious attention. They turn out to be directed towards the reinstatement of an earlier state of things. We may assume that as soon as a given state of things is upset there arises an instinct to recreate it, and phenomena appear which we may call 'repetition-compulsion.' Embryology, for instance, is nothing but a repetition-compulsion."

Thence by wordy transition the author brings the reader to a "death instinct," opposed to the "erotic instincts, which are always trying to collect living sub-substance." In other words, he has simplified everything in terms of instinctual catabolism and anabolism. It reads very glibly and sounds important, but unfortunately his original use of the word instinct is incorrect; biologists for many years before Freud have defined the word, and an instinct certainly does not "arise from sources within the body"; it does not "arise" at all. It is an inherited pattern of behavior, set off by either external or internal stimuli, and its object is racial or individual survival. Freud's discussion really has nothing to do with instincts, but goes on to juggle with biologic phenomena of a much lower order of integration, and, finally, with a conception as vague as Bergson's *élan vital*. The discussion has only one merit—it demonstrates the futility of Freud's attempt to defend "the independence of psychology from all other sciences" and of his attitude that psychology is not a part of biology. He fails to convince one that "the organic world" can be separated from the "psychological."

Lecture XXXIII is a dogmatic explanation of the psychology of women; in the last analysis everything comes down to "penis envy." It is stated early that "this chapter contains nothing but observed facts," yet pages 174 to 178 read like an exposition of a quiet speculative theory built up from analytic experience. Of course one has no right to be too dogmatic as to what is and what is not "an observed fact." Freud's attitude is that the intellectual nihilists have gone too far; he believes that contact with practical life is the best criterion, and most persons agree that if a theory works it probably approximates truth. When the methods of observation are of necessity decidedly subjective, and when many interpretations may be given to the same observations, it would seem wise to proceed tentatively; in fact, Freud states: "If you accuse me of having an *idée fixe* on the subject of the influence exercised by the lack of a penis upon the development of femininity, I cannot of course defend myself."

The last lecture, "A Philosophy of Life," has not much to do with analysis, but it contains a courageous discussion of the relation of science to religion and an illuminating description of the "God the Father" conception of certain religions.

The plea for scientific work in psychology is pertinent, and the attack on scientific nihilists helps one to keep one's feet on the ground. The discussions of Marxism and Bolshevism are trite. One applauds the sentiment that "Our best hope for the future is that the intellect—the scientific spirit, reason—should in time establish a dictatorship over the human mind."

On the whole, the lectures, although stimulating and well written, are disappointing. The translation is smooth, but in some places one feels that the sense is not accurately transmitted.

All the world accepts Freud as a leader; the discussion as to whether or not psychoanalysis can be admitted to the fold of the "sciences" (more or less "exact") is unimportant. What one must remember is that all knowledge and all theories are approximations. President Dodd of Princeton University, in the Harvard Alumni Bulletin of July 6, 1934, expressed this idea well: "The methodology of science is experimentation. Its conclusions rest on the study of numerous cases with a skeptical and objective eye, with the findings carefully recorded and compiled. . . . However, when we seek to apply this method to the so-called social sciences, peculiar difficulties emerge . . . one steps into a field heavily charged with feelings. . . . Man's social nature is complex and elusive, and no contributions of science have reduced the value of the tolerant mind in the treatment of social ills or the need for the keen imagination tempered by intellect which illuminates the dark passages in social progress. Social data arranged in neat statistical tables serve good purposes, but supply no substitutes for great minds of penetrating intuitive power."

Psycho-Analysis and Medicine: A Study of The Wish to Fall Ill. By Karin Stephen, M.D., M.R.C.S., L.R.C.P. Price, $2.50. Pp. 238. New York: The Macmillan Company; Cambridge, England: Cambridge University Press, 1933.

New presentations on psychoanalysis are welcome, particularly when they are based on clinical experience and also when they tend to bring the field closer to general medicine. This book is a decided contribution along such lines in that the author endeavors to show how nervous or mental illness may be an expression on the part of the patient of a wish to be ill in order to escape from the more uncomfortable fundamental difficulty. Some of the comments showing the purpose of this work are:

"Neurotic symptoms are defenses designed to prevent anxiety from developing when repression threatens to give way. . . It is claimed that psychogenic illness is a piece of behavior as purposive as putting up a hand to ward off a blow. The purpose of this kind of illness is to prevent anxiety from developing." Psychoanalysis, despite the exuberance of some of its converts, is not a gospel but an empirical science, building up general laws on the material it observes. "The method imbued in psychoanalysis has one important point in common with other scientific procedures, and that is that it is objective. . . The foundations of psychogenic illness always date from the early conflicts between desire, disappointment and fear in childhood. . . There are then, two very formidable difficulties in understanding the reasons for falling ill; difficulties of an emotional rather than of a purely intellectual kind. The first is that these reasons are unconscious and the patient himself does not know anything about them and not only does not know but does not want to know and even falls ill on purpose one might say in order not to know." The second is "that we, the investigators do not want to know either. . . It would be painful for us . . . such things arouse defenses."

The book is largely made up of lectures given by the author to medical students. The material is presented simply and in great detail. The book may be described as being one of the soundest to read for an understanding of what psychoanalysis really means, as well as for its value in demonstrating how illness of any sort may be serving a definite purpose for the patient. It probably will not be accepted in its entirety by either extreme defenders or by antagonists of psychoanalysis, but

it is to date the best presentation on the fundamental meaning and uses of psychoanalysis as a clinical psychotherapeutic entity. A valuable addition in the make-up of the book is the exact and inclusive summaries at the end of each chapter.

Wish-Hunting in the Unconscious. By Milton Harrington, M.D. Price, $2.50. Pp. 189. New York: The Macmillan Company, 1934.

The subtitle of this book states that it is "An Analysis of Psychoanalysis," and three quarters of the volume is devoted to a criticism of Freud's tenets, showing the weakness of his theoretical formulations and the limitations of his method in clinical work. The main pragmatic objection to psychoanalysis is that it gives no directions for "right living" and thus makes no sound contributions to the field of mental hygiene. There is no question but that there is need of a scholarly and critical review of psychoanalysis. Unfortunately, the book fails in this aspect, as the criticism is sketchy and deals largely with Freud's earliest works, without touching on the latest developments in the more philosophic aspects of the psychoanalytic theory. In this respect it is far inferior to Jastrow's work. The last part of the book is given over to Harrington's constructive philosophy, which he calls "the alternative to psychoanalysis." He divides it into three parts—psychophysiology, psychopathology and mental hygiene. He describes his philosophy as purely mechanistic and dealing in terms of what is actually known rather than in terms of the speculative and fanciful. He admits that the mechanistic point of view cannot give much understanding, as physiology has not yet been able to explain human behavior, motivation and conduct. He believes that he has the right to take a few outstanding physiologic facts and on the basis of these construct a diagrammatic scheme that would fill in the gaps, drawing the parallel from the fact that although one may not know what electricity is, one may nevertheless know how to utilize it to the best advantage.

Harrington's point of view is so naïve that it does not seem likely that he wholeheartedly subscribes to it. Various simple schemes and "common-sense" ideas have been put forward a great many times to explain such complex phenomena as the neuroses and mental disease, and yet every clinician knows that human ideation is so complex that any simple scheme cannot account for it. The value of psychoanalysis lies in the fact that although it has definite limitations as a therapeutic method it has nevertheless provided definite evidence of the enormous complexity of thought processes, especially in relation to emotional life, even though some of the explanations offered by it may be untrue. The alternative to psychoanalysis that Harrington offers—"mental hygiene"—is so vague, diffuse and general that it has no greater scientific basis than psychoanalysis; at the same time, it has none of the virtues and understanding of human behavior that psychoanalysis has provided. One can well imagine that there might be some good and workable alternatives to psychoanalysis, but these have not been brought out by the author.

The Physical Mechanism of the Human Mind. By A. C. Douglas, M.B., Ch.B. Hon. Surgeon, Dunfermline and West Fife Hospital. Price, $5.25. Pp. 251, with 24 illustrations. Baltimore: William Wood & Company, 1934.

In this interesting book Douglas tries to demonstrate "that by taking full advantage of the latest advances in physiological knowledge the gaps left by Associationism may be filled, the criticisms and requirements of Gestaltism may be met, and a complete scientific theory of Mind may be presented, upon the materialistic basis which Behaviourism rightly demands."

The first nine chapters are devoted to the presentation of an admittedly incomplete array of material, on which the author constructs his thesis. This material deals with some of the facts of comparative neurology (evolution), neuro-anatomy and neurophysiology; Lapicque's hypothesis of chronaxia is extensively used in the description of the mechanism of reflexes by means of interesting diagrams. The author fails to mention the works of Dr. H. H. Donaldson on the growth and development of the brain and the fundamental investigations of Dr. G. E. Coghill

and Dr. Angulo y Gonzales on the correlation of behavioral development with anatomic structures. The inclusion of the conclusions from these investigations would have added greatly to the support and elucidation of the author's thesis.

The last seven chapters are devoted to the construction of a "scientific synthesis" of mind based on the partly prepared material of the previous chapters. Douglas discusses attention, perception, association, memory, thought, knowledge, belief, reason, will, imagination, logic, speech and truth. These phenomena are analyzed and correlated with the facts of neuro-anatomy and neurophysiology. "Upon the cortical network, interlaced in inconceivable intricacy with preregistered perception-patterns, falls the incessant bombardment of continuous volleys of environmental and organic stimuli, and the interplay of the reactions aroused, with the shifting and shading of their accompanying phases of consciousness, with the conflict of their varying tendencies to action, constitute the whole phenomena of mind." This is, of course, a pragmatic common sense disregard for the great problem concerning the nature of the link between "nerve-process and mind-process." However, many will agree with Douglas that it is "the failure of psychology to correlate its data with material processes and physical laws that constitutes the barrier to scientific acceptance."

Modern Clinical Psychiatry. By Arthur P. Noyes, Superintendent of the State Hospital for Mental Diseases, Howard, R. I. Price, $4.50. Pp. 485. Philadelphia: W. B. Saunders Company, 1934.

Textbooks of psychiatry are becoming more numerous and are steadily improving in scope and character. This book is no exception to the trend. It is a welcome addition and will prove of definite value as a book for clinicians and students. Noyes states in the preface his point of view regarding behavior as representing the integrated response of the organism and has constructed the textbook on a psychobiologic basis in terms of the total integration of the organism. This is a sound approach for any psychiatric text at this stage of the development of the field of psychiatry. The material shows a great breadth of view and acceptance on the part of the author. He presents fairly the different theories, as well as the different descriptions applied to an understanding of psychiatry and its clinical syndromes.

The first seven chapters deal with the preparatory discussion on the causes and nature of mental disorders and their symptoms. This section should prove to be of particular value to medical students in the preclinical years. The remainder of the book deals with the examination of patients, the later chapters taking up the different clinical syndromes. The book is not too technical and not too detailed. The technical material is discussed in a manner common in medical books in general and emphasizes in this way that psychiatry is a branch of medicine and should be studied and dealt with as such.

There is nothing particularly original or special that sets this book out as being markedly different from others. Even for this reason it achieves distinction, for it will exist as a fair, complete, useful aid, easily understandable and unusually inclusive and comprehensive. In chapter 6, which deals with the psychoneuroses, Noyes accepts them as "minor" psychoses, which he considers a better name, as it is difficult to establish a true definition between neuroses and psychoses.

The general make-up of the book is excellent. The index is better than that usually found in a text of this nature. The bibliography at the end of each chapter is inclusive and shows that there has been a thorough investigation of the subject. The book is correctly titled, being definitely modern, and exactly clinical in all phases of its material.